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Advanced Pharmacological Uses of Medicinal Plants and Natural Products

Ajeet Singh, Padam Singh, and Navneet Bithel

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Advanced Pharmacological Uses of Medicinal Plants and Natural Products

Ajeet Singh
National Dairy Research Institute, India

Padam Singh
Vaccine and Infectious Disease Research Centre, Translational Health Science and Technology Institute, India

Navneet Bithel
Gurukul Kangri University, India

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Medicinal plants are a great source of medicine for treating various human ailments. Traditional use of herbal medicine, which was developed within an ethnic group before the development and spread of modern science, is the very basis and an integral part of various cultures. Different medicinal systems throughout the globe are still operational and use natural herbs for treating diseases. Traditional Chinese Medicine (TCM), Ayurveda, Kampo, Traditional Korean Medicine (TKM), and Unani are some commonly found traditional medicinal systems in use today. They are used directly, or their secondary metabolites are used as anti-bacterial, antifungal, immunomodulators, anti-hair fall, and multiple other purposes. However, their blood purification properties prevent blood from toxicity. Hundreds of medicinal plants are used in Ayurveda for blood purification, particularly plants which are astringent or bitter (pungent or sharp tastes). In addition, medicinal herbs do not have side effects.

Medicines of plant origin have been used for treating humans and animals without any adverse effects. New medicinal plants are searched to develop more effective and cheaper drugs in place of synthetics drugs. Plants represent a large natural source of compounds that might serve for the development of novel drugs. Currently medicinal herbs are researched for diuretic properties, and several medicinal herbs are used as diuretics. Currently various synthetic medicines are available for this purpose; however, natural resource medicines are still an important choice because of their higher efficiency and better safety. Further, some herbs are also important sources of antioxidants, which protect the body from the effects of free radicals produced in the body. Antioxidants are required by our body due to increase in the likely exposure of the body to harmful pollutants, radiation, UV lights, etc. These have the ability to delay the oxidation, and plant-derived products are of great interest due to the adverse effect of antibiotics.

Breast cancer (BC) is sub-categorized into several well-recognized subtypes including estrogen receptor (ER), progesterone receptor (PR), and HER2 triple-negative breast cancer (TNBC). It is a heterogeneous disease entity constituting about 15% of breast cancer cases worldwide. TNBC is associated with poor prognosis and lack of sustained response to conventional chemotherapeutic agents. Although no approved targeted therapy is available for TNBCs, molecular-profiling efforts have revealed promising molecular targets such as the Wnt/β-catenin, STAT3, VEGF, EGFR, polyadenosine ribose polymerase inhibitors (PARPi) and DNA repair pathway, androgen pathway, and NOTCH pathway. Moreover, more research needs

to be performed in the area of TNBC aiming at dissecting potential pathways and identifying potential molecular signatures to develop new targeted biologic modifiers. Natural agents are the abundant chemical compounds available from diverse plants. The authors aimed to summarize the current evidence and discuss the natural agents that target TNBC using different pathways.

The peptic ulcer is a widespread and common health problem around the world. The major causes include generation of free radicles, decrease in mucosal defense factor, or increase in mucosal injurious factors. Various plants and their products have been known to prevent or reduce peptic ulcers. Natural products from plants are a rich resource used for centuries to cure different ailments. The use of phyto-constituents as drugs has proved to be clinically effective and less toxic than existing drugs. An attempt has been made to review some plant species and their products as phytomedicines showing promising results in prevention and treatment of peptic ulcers.

Extensive research suggests that a number of plant-derived chemicals and traditional Oriental herbal remedies possess cognition-enhancing properties. Widely used current treatments for dementia include extracts of Ginkgo biloba and several alkaloidal, and therefore toxic, plant-derived cholinergic agents. Several non-toxic, European herbal species have pan-cultural traditions as treatments for cognitive deficits, including those associated with aging. Acute administration has also been found to reliably improve mnemonic performance in healthy young and elderly cohorts, whilst a chronic regime has been shown to attenuate cognitive declines in sufferers from Alzheimer's disease. The present chapter looks at the ethnobotanical and pharmacological importance of various plants cognitive enhancing and other neuroprotective abilities.

Section 2
Role of Medicinal Plants in Microbial Diseases

Malaria is a life-threatening infectious disease caused by a protozoan parasite of the genus Plasmodium. It is transmitted through the bites of infected female Anopheles mosquitoes. The global burden is estimated to be around 219 million cases in 87 countries. Natural compounds have been used primarily in the traditional medicine for thousands of years. For the treatment of malaria, natural products were used until the development of synthetic drugs, and most of the currently available anti-malarial drugs have been derived based on the compounds from these traditional medicinal plants. The current chapter tries to briefly indicate the emerging resistance against anti-malarial drugs and to discuss the recent research on natural products that have been evaluated for anti-malarial activity. Rigorous evaluation of the efficacy and safety of traditional medicines is required along with identification of active constituents in order to develop new drugs with novel mechanisms of action.

Medicinal plants have been necessary to conventional and non-customary types of prescriptions dating back to somewhere around 5000 years ago. Researchers progressively depend on current logical techniques and proof-based medication to demonstrate the viability of herbal medicines and spotlight on a better comprehension of the systems of their activity. Notwithstanding, data concerning quantitative human health advantages on natural remedies is yet uncommon, constraining their legitimate valuation. Traditional medicines are regularly utilized for the wound-healing process covering a wide zone of various skin-related infections. This chapter will give information about the wound-healing capability of plants that are useful for the advancement of new wound-healing formulations.

Curcumin, the polyphenol natural product, is a constituent of the traditional medicine known as turmeric. Extensive research over the last 50 years has indicated that this polyphenol displays potent pharmacological effects by targeting many critical cellular factors through a diverse array of mechanisms of action. However, there are some obstacles that prevent this wonder molecule to be effective in clinical settings and limit its use to topical applications only. Curcumin has recently been classified as both PAINS (panassay interference compounds) and an IMPS (invalid metabolic panaceas) candidate. Due to likely false activity of curcumin in vitro and in vivo has resulted unsuccessful clinical trial of curcumin against several disease. The chapter will review the essential medicinal chemistry of curcumin as well as envisage a compilation and discussion on the poor bioavailability of curcumin.

Chapter 13

The medicinal plants have been used by humans since ancient times, and the great civilizations of the world in ancient times were well aware of the benefits brought by the use of medicinal plants. This chapter provides important information regarding medicinal plants that have a wide variety of antioxidative agents ranging from bitter compounds that stimulate digestion system, phenolic compounds for antioxidant and numerous other pharmacological properties, antibacterial, and antifungal to tannins that act as natural antibiotics, diuretic substances, alkaloids, and so forth.

Chapter 14

Because bryophytes are a promising source of a large number of secondary metabolites, they are used efficiently in surgical dressing, herbal medicines, antibiotics, and other pharmaceutical products. The advent of several biotechnological tools and their utilization in the exploitation of pharmaceuticals properties of bryophytes leads to a new era of bryo-pharmaceuticals. Nowadays, the biopharmaceutical productions using moss system are gaining importance over other plant systems because of their unique properties such as predominant haploid gametophytic stage, stable gene integration, efficient secretary signals, and large-scale production in

bioreactors. Several researchers have established moss system as safe and efficient for the production of several complex modified recombinant pharmaceuticals under standard conditions. The moss Physcomitrella patens are extensively exploited and commercialized as a production host for production of several recombinant proteins, human growth factors, antibiotics, and its derivatives.

Section 4
Plant-Specific Pharmacological Utilizations

Plants have been a source of treatment and a cure to various diseases and health conditions. India has immense traditional knowledge of useful plants of medicinal importance. This knowledge has been an intrinsic part of the lifestyles of various indigenous peoples in different parts of the country and has served as the basis of discovery/designing of modern medicines. One such region rich in traditional knowledge of medicinal plants is the north-east Indian state of Manipur. Eupatorium birmanicum DC known as Langthrei (Asteraceae), which is grown in every household and has a revered position, has anti-ulcer properties, and crushed fresh juice is taken orally to treat gastro-enteritis. There is an abundance of such ethnomedicinally important plants whose improved scientific understanding will improve their value in treating chronic conditions as well as conserving the plants and their knowledge. This chapter emphasizes the importance of E. birmanicum, discussing its various medicinal properties.

Traditionally, the gum resin produced from the Boswellia serrata plant has been used in as a therapeutical compound. The gum that contains a chemical known as boswellic acid, AKBA (3-O-acetyl-11 keto-β-boswellic acid), and widely in ayurvedic medicines. This is used to treat the disease like reduction in various inflammatory conditions of the skin, eye, as well as respiratory disorders such as asthma, bronchitis, and laryngitis. The boswellic acids were also found capable to inhibit both hemolysis and chemotaxis of leukocytes and were shown to work by inhibiting C3-convertase, a key enzyme of the classical complementary pathway. In

addition to this, the compound shows beneficial effects in various pharmacological properties like immunomodulation activity, polyarthritis, activity against Hepatitis C-virus and other harmful microbes, Colitis and Crohn's disease, and so on. The boswellic acid is also used to treat patients with memory disorders. In this chapter, the chemical nature and isolation of boswellic acid and its therapeutic importance have been highlighted.

Phytochemicals have recently been studied in vivo for their unmatched interactions in curing lethal diseases that can't be cured by allopathic medical intervention without any adverse effect on the patient health. These methods were being used in ancient India, where Jamun and Giloy have been used to decrease hormonal imbalance and pathological disorders. Signaling pathways of the active components of Tinospora cordifolia thus enable effective disease targeting. With so much to offer to the scientific world of medicine, the plant Tinospora truly acts as an incredible source as it deals with seasonal fever like Dengue, Malaria, Chickengunia, and anticancer and anti-HIV (research undergoing). Whereas the Syzygium cumini (Jamun) fruit and seed hold worth in treating various diet-related malfunctions, especially hyperglycemia. In the current research, Jamun seed and fruit extracts have been proved effective in the regulation of blood glucose and insulin parameters.

Preface

Medicinal plants and herbal medicines can be applied for pharmacognosy, or the discovery of new drugs, or as an aid for plant physiology studies. In recent years, there is increased interest in the search for new chemical entities, and the expression of resistance of many drugs available in the market has to lead to a shift in paradigm towards medicinal research.

This book is about spreading the knowledge of herbal medicine being used for human welfare from ancient times. Herbal medicines provide health benefits without side effects as compared to the chemical drug being used to treat health problems nowadays. The field of drug discovery is looking for new chemical entities (NCE) for the effective treatment of human health problems without any side effects, toxicity, and drug resistance. The knowledge of medicinal plants and natural products in this book would help the researcher working in new drug discovery from natural sources.

The constantly changing landscape surrounding modern pharmacological and medical microbiological science makes it challenging for experts and practitioners to stay informed of the most up-to-date research. That is why IGI Global is pleased to offer this two-volume comprehensive reference collection that will empower students, academicians and researchers with a strong understanding of these critical issues by providing both broad and detailed on cutting-edge theories and development. This compilation is deliberated to act as single reference source on conceptual, methodological and technical features as well as to provide insight into emerging trends and future prospective within the discipline.

Pharmacological uses of medicinal plants and natural products is organized into three sections that provide comprehensive coverage of important topics. The sections are:

Role of Medicinal Plants in Human Physiological Disorders
Role of Medicinal Plants in Microbial Diseases
Bioactive Compounds and Natural Products
Plant-Specific Pharmacological Utilizations

Although the primary organization of the contents in this book is based on its four sections, offering a progression of coverage of the important concepts, methodologies, technologies, innovations, applications, utilizations, and emerging trends, the reader can also identify specific content by using the extensive indexing system listed at the end.

As a comprehensive collection on the latest findings related to pharmacological and microbiology, this publication provides students, academicians, practitioners, and researchers with a complete understanding of the development of applications and concepts surrounding these critical issues.

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Ajeet Singh
National Dairy Research Institute, India

Padam Singh
Vaccine and Infectious Disease Research Centre, Translational Health Science and Technology Institute, India

Navneet Bithel
Gurukul Kangri University, India

Section 1
Role of Medicinal Plants in Human Physiological Disorders

Chapter 1
Traditional Medicinal Systems:
Their Role and Place of the Strategies for Blood Purification in Human Beings

Aashaq Hussain Bhat
Chaudhary Charan Singh University, Meerut, India

Shahla Nigar
Mahatma Jyotiba Phule Rohilkhand University, Bareilly, India

ABSTRACT

Medicinal plants are a great source of medicine for treating various human ailments. Traditional use of herbal medicine, which was developed within an ethnic group before the development and spread of modern science, is the very basis and an integral part of various cultures. Different medicinal systems throughout the globe are still operational and use natural herbs for treating diseases. Traditional Chinese Medicine (TCM), Ayurveda, Kampo, Traditional Korean Medicine (TKM), and Unani are some commonly found traditional medicinal systems in use today. They are used directly, or their secondary metabolites are used as anti-bacterial, antifungal, immunomodulators, anti-hair fall, and multiple other purposes. However, their blood purification properties prevent blood from toxicity. Hundreds of medicinal plants are used in Ayurveda for blood purification, particularly plants which are astringent or bitter (pungent or sharp tastes). In addition, medicinal herbs do not have side effects.

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INTRODUCTION

Medicinal plants from ancient times have been appreciated and observed as great gifts of nature. Their uses for curing numerous infections and illnesses have been found in all cultures from times immemorial. In the treatment of traditional diseases, naturopathic doctors prescribe medicines made from natural products like herbs, mixture of herbal components, herbal preparations, and flawless herbal products. The use of natural remedies for treating infections have been widely followed by descendants of most countries throughout the globe. In India, the widely followed traditional medicine systems include Unani and Ayurveda. In China, people usually follow and use both traditional medicines and allopathic medicine equally to diagnose, treat and prevent human ailments (Holtz, 2007). Several nations, especially developing countries of the world make use of traditional medicinal system for pharmacological purposes, and 70–95% of the population depends on these traditional medicines for their primary health care. In Mali and most other African countries, 75% of the people living there rely on herbs and their products for treating diseases and as a primary health care (Imperato, 1981). In preparation of these natural drugs, hakims or doctors usually use the entire plant or its different parts like leaves, roots, stems, bark, branches, seeds, etc. In addition, some of the remedies are prepared from excretory plant compounds such as gum, resins and latex and prove effective in treating patients suffering from several illnesses. Most of the people usually prefer to use natural remedies for treating diseases, and try to avoid the extensive use of synthetic drugs and antibiotics because of their associated health risks and toxicity. Scientists throughout the globe pay great attention in the use of these herbal preparations and products to treat people in order to reduce the use of hazardous synthetic drugs.

The use of medicinal plants for preparation of medicines for human use goes back to at least 60 thousand years as per fossil records and spread throughout the globe. In traditional medicinal systems, people use raw natural products and use them as a curative of different human sicknesses and infections. Different traditional medicinal systems operational in different countries like Traditional Chinese Medicine (TCM), Ayurveda, Kampo, Traditional Korean Medicine (TKM), Unani etc. make use of plant derived products or their different parts for preparing herbal medicines from ancient times and are still in use by most people. These distinct types of medicines have certain shortcomings and weaknesses, but they are still a valuable store-house of human knowledge (Fabricant *et al*., 2001; Alves & Ross, 2007; Shi *et al*., 2010).

In economically weak developing and underdeveloped countries, the strategies for use of herbal plants are mostly allied with sorcery and delusion due to lack of scientific knowledge about the medicinal values and therapeutic actions of plants. The live illustration of this is the Doctrine of Signatures, and basics of which are

known in many healing cultures of the world (Boehme, 1982). The Doctrine of Signatures is built on the hypothesis that the appearance of plants may give signs to their medicinal properties- it is explained as God's mark on the plant. Sometimes, this concept however works, but still based on myths and illusion (Gurib-Fakim, 2006).

Blood which is referred to as river of life is an imperative transporter of nutrients and oxygen to all parts and organs of our body and thus helps in accurate functioning of each organ. However, this blood gets impure due to various ways like obesity, diabetes, hormonal imbalance, unbalanced consumption ways, late night sleeping habits, eating oily rich and junk foods etc. which ultimately affect human well-being and lead to several dreadful diseases. Medicinal herbs are used directly or indirectly in blood purification, to prevent the rapid transfer of infections, toxins, bacteria, viruses and other impurities in the body. Blood transports oxygen and nutrients to all parts of the body and does not function on its own, and thus it is clear that if blood contains unwanted and destructive impurities, they too may be carried through blood to various parts of the body and can cause damage to integral organs. While on the other side, routine body detoxification gives a healthy kick start to our metabolism and immunity which helps to live healthy and extended lifespan with comfort.

MEDICINAL PLANTS AND THEIR MEDICINAL IMPORTANCE

The term "medicinal plant" comprises of different types of plants used in "herbology" or "herbal medicine." The term "herb" has been derived from the Latin word, "herba" and an old French word "herbe". Now a days, botanists consider herb as any portion of the plant like fruit, seed, stalk, bark, floret, foliage, stigma or a root, as well as a non-woody plants or their parts. Formerly, the use of this term "herb" was only applied to non-woody plants, including those that come from trees and shrubs. Apart from these medicinal values, these plants are also directly used as food, flavonoid, drug or fragrance and in certain divine activities. A medicinal plant or herb can thus be defined as "any plant or herb which contains diverse ingredients and secrete metabolites which are pioneer for the production of useful remedies having therapeutic values".

Medical importance of different flora has been known from prehistoric times. The use of herbs in treating diseases has been found in Ancient Unani manuscripts, Egyptian papyrus and Chinese writings. It is evident that from over 4000 years, Unani Hakims, Indian Vaids, Europeans, Chinese, Korean and Mediterranean cultures were using herbal plants as medication. Many of the countries where indigenous cultures exists such as Rome, Egypt, Iran, Africa and America used herbs in their therapeutic rituals, while in other established traditional medical systems such as Unani, Ayurveda, Kampo, Traditional Korean Medicine and Chinese Medicines,

herbal remedies were used thoroughly. These various traditional medicinal systems are still operational in many parts of the world. Their continued usage in many parts of the world for treating several human infections and diseases may have arisen due to increase in human population, shortage of drugs, unnecessary cost of treatments, ill effects associated with using synthetic drugs, resistance development against some synthetic drugs for treating infectious, diseases and other human ailments.

Among early cultures, India has been well known to be a rich storehouse of therapeutic plants. Numerous medicinal and aromatic plants are found in Indian forests and are collected from their principal storehouse for their use in the manufacture of medicines and perfumery goods. In AYUSH systems in India, about 8,000 herbal remedies have been codified. The major systems of indigenous medicines followed include Ayurveda, Unani, Siddha and Folk (tribal) medicines, and in India, among these systems, Ayurveda and Unani prescriptions are most widely followed and extensively practiced. The use of herbal medicinal remedies for treating humans has increased and according to report by World Health Organization (WHO), it has been found that about 80% of people worldwide rely on these medications for some aspect of their primary health care. Further, WHO in its report has found that around 21,000 plants have been investigated for having medicinal properties against different infections and diseases.

Different medicinal plants and their products are used for treating different human infections and diseases. However, this chapter will focus on the role and place of medicinal plants in the tactics for blood purification and a note on traditional medicinal systems.

Traditional Medicinal System

From the fossil records and ancient writings, it is concluded that Traditional Medicines (TM) are the ancient form of health care in the world and are practiced in the deterrence, and curative of physical and mental illnesses. Throughout the globe, people tried and practiced various fruitful healing methods to overcome different health and life threatening diseases. TM is recognized by different names in different nations and still is practiced in many countries today (Abdullahi, 2011; WHO, 2000). In TMS, medicines used for healing and treatment of different diseases are mostly produced from herbal plant parts and before their use for treatment of human diseases, are first given experimental trials. The different traditional medicinal systems used in different countries are discussed in brief.

In China before sixteen century, Traditional Chinese Medicine (TCM) was considered as the leading procedure of medical care (Dong, 2013) and it continued till nineteenth century, however, this medicinal system still appears in Chinese medicinal system, and it is continually being investigated. It is believed that TCM

is to be more than 5000 years ancient, having relatively good medical rehearsal and familiarity, and is rich in records from "clinical experiments" which assured its usefulness and efficacy. This ancient system of medicine is created on two discrete concepts namely yin and yang, and the five fundamentals which describes about the natural laws that govern good health and longevity (Kapoor, 1990; Patwardhan, 2005). The records of TCM were written by ShenNung, however, the Modern Day encyclopedia of Chinese *material medica* published in 1977 is the comprehensive citation of Chinese herbal prescription. The encyclopedia lists that out of nearly 6000 medicines, 4800 medicines are used for human use (Magner, 1992). The information about the TCM has been acquired through clinical experiments and has paved a way in the development of new effective drugs. TCM now is not only component of Chinese public health, but has been practiced in other countries, especially in western countries as a complementary or alternative medicine and currently, 1.5 billion follow this health care system (Qi *et al.,* 2013; Dobos *et al*., 2005). The medicines in TCM are prepared by combining desired proportions of several herbs and ingredients according to strict rules, commonly referred to as formulas. The formula usually consists of four elements viz., "monarch", "minister", "assistant", and "servant" and each of these have different roles in the formula, thus form drugs with diverse medical properties. These drugs basically possess organic group, responsible for the desired medicinal and therapeutic properties, thus reducing adverse reactions (Zhang *et al*., 2013). The popularity of treating diseases and infections with herbal remedies has emerged because of positive results being achieved by following TCM in other countries of the globe. The commonly used plants in TCM include *Angelica polymorpha* var. *sinensis*, *Artemisia annua*, *Ephedra sinica*, *Paeonia lactiflora*, *Panax ginseng* and *Rheum palmatum* (Magner, 1992; Padua de, 1999; Gurib-Fakim, 2006).

Another traditional medicine is Kampooperating in Japan. Its history goes back to the fifth and sixth centuries, and it was the time when Chinese TCM was followed in Japan. However, Japanese practioners have considerably modified the TCM and followed it whenever they felt need of it so as to meet their demands and finally new medicinal system emerged in Japan, now referred to as Kampo (Watanabe *et al*., 2001). Studies have shown that some physicians in Japan follow Kampo medicines in their routine life, which may be commonly referred as medication (Yakubo *et al*., 2014; Mogami & Hattori, 2014). Doctors in Japan treat their cancer patients by employing Kampo medicines along with radiotherapy or chemotherapy, and thus, focusing on use of integrated modern western medicine and TM (Yakubo *et al*., 2014; Yu *et al*., 2006). The continuous use of Kampo medicines along with western medicinal systems has resulted in growing need to study the interactions between these types of medications (Zhang *et al*., 2013).

In Indian subcontinent, two most widely followed traditional medicinal systems, Ayurveda and Unani medicine are in use from an ancient Greek holistic medical system whose history goes back to over 2500 years (Lone *et al*., 2012) and are believed to be the most earliest of all medicinal ethnicities. Its history is older than TCM and is regarded as start of systemized medicine. Great scholars like Dioscorides and Hippocrates have also been influenced by Ayurveda and have taken many of their philosophies from India. There is no record of western medicines in ancient Hindu writings; however, the text of Greek and Middle Eastern literature gives clues about the concepts and drugs of Indian origin (Chopra, 2000). Ayurveda is derived from the Sanskrit words 'Ayur' which means life and 'Veda' meaning knowledge or science and hence it means the science of life, therefore, ayurveda is regarded as the tool for attaining decency (dharma), prosperity (artha) and pleasure (sukha). In India, knowledge and wisdom have been given much importance and has transferred on from one generation to another through melodies and poetries, which scholars and physicians had to pick up and narrate by heart. The Veda, which is considered as the word of God in Hindu religion is the oldest scripture, consisting of four parts Rig Veda, Sama Veda, Yajur Veda and Atharva Veda, the earliest of which dates back to 2000 years BC. The records of ayurvedic medicine and the medicinal uses of plants are documented in various lyrical hymns in the Rig Veda. In India, the first school where knowledge regarding ayurvedic medicine was taught in 500 BC was the Banaras Hindu University and here the great Samhita (or encyclopedia of medicine) was written. Later after 700 years, another great encyclopedia was published and these two Samhitas form the basis of the Ayurveda in Indian culture (Chopra, 2000). This types of medicinal system is believed to be similar to Galenical medicine as both of these are centered on dosas (body humors) and prana (inner life force) that play vital role in maintaining digestion and mental activity. The biotic and abiotic components of ecosystem, along with hominids are essential constituents of prithvi (earth), jada (water), tejac (fire), vaju (air) and akasa (space). The people who follow these traditional medicinal systems give their keen interest in learning the concept of impurity and cleansing. The imbalance between these different elements results in illness and as a result, there feels is a need to restore this balance (Magner, 1992). The most popular medicinal plants used in Ayurveda include *Azadirachta indica* (neem), *Rauwolfia serpentina*, *Centella asiatica*, *Cinnamomum camphora*, *Santalum album*, *Terminalia* sp., *Elettaria cardamomum* and *Withania somnifera* (Kapoor, 1990; Padua de *et al.,* 1999; Gurib-Fakim, 2006). The much awareness about the used traditional medicines all over the world started since mid-1970s when WHO laid much emphasis on traditional medicine and in India, Unani has attracted substantial courtesy and had incorporated into the national health care system (Parasuraman *et al*., 2014). People throughout the world are still using traditional medicine for health care (Lu, 2013) and its usage differs in different countries (Boakye *et al*., 2015). In

some countries like Africa, 80% of the human population use TM-either alone or in combination with conventional prescriptions (Oliver, 2013). However, in Australia TM is in risk of disappearing due to the incidence of conventional medicines, and in Israel TM is substituted by current allopathic medicines (Lev, 2006). Although, some specialists are of the view that traditional medicinal systems are of little consistency, still they are used by most of the populaces in the world (Lu, 2013).

TRADITIONAL SYSTEM OF MEDICINES WITH ASPECTS OF BLOOD PURIFICATION

Blood cleaning is one of the most essential munitions in the alternative health storehouse for bringing out optimum wellness and defeating cancer. The role of blood purifier has been traditionally used up for clearing morose circumstances such as cysts, abscesses, acne and skin frenzied diseases like chicken pox and measles. Conventionally, they are measured as ameliorate of anticancer and other threating diseases.

In our life styles, we come across with the various toxins that are usually found in food, air and water. The hepatic system is overwhelmed by food additives, water pollutants and lack of nutrition which work together to damage the liver. Keeping in view of such type of circumstances, it is not surprising that these simple and small lesions or pimples on body give way to cancer, which is a more drastic disease.

HERBS THAT STIMULATE TO ABOLISH TOXINS FROM THE BLOOD ARE KNOWN AS "BLOOD PURIFIERS"

The herbs generally having blood purifying properties are usually sour in taste and they contain natural soaps known as "saponins". These saponins are helpful or functional in rupturing the damaged or decayed red blood cells (erythrocytes) to release iron, vitamins and other nutrients contained in them so that they can be "recycled" or reutilized in making fresh red blood cells, to enhance iron utilization and bio-availability. They also enhance the absorption of nutrients and many vitamins like vitamin A, B and C across the intestinal lining. Many of the blood purifiers are also known as alternatives. The term alternative is used because many blood purifiers alter the chemistry or composition of blood. These alternatives or blood purifiers boost up the body skill by enhancing the flow of bile from gall bladder and eliminate toxins through the liver and also from the kidneys. However, they do not produce a noticeable purgative action.

Blood Purification Through the Natural and Herbal Approaches

The buildup of toxins in the blood is due to less labour and physical activities, superfluous eating of healthy foods and surplus consumption of animal proteins. All these toxic substances penetrates into the cascade system of blood from the liver, which is our detoxifying organ of the body. There are many different types of cleansing herbs that are processed in a traditional manner to get rid of various toxins from the liver, kidney and lymph system and ensuring immaculate blood circulation through the blood stream. Mainly the herbal additives are recommended to be consumed by any individual, as these additives do not cause any of the side effects or aftereffects. The various plants known for the blood purification activities are discussed below.

Arctium lappa Linn. (Asteraceae)

Arctium lappa have been especially valuable in the blood cleaning and smoothening of skin properties. It has been an important botanical and traditional Chinese medicine and Western folk herbalism. In Asia, usually in Japan the whole plant is edible and popular vegetable. In recent years, it has also been used as an additive of hair tonics and as a cosmetics for maturing of skin (Stephlina, 2015).

Taraxacum officinale (Linn.) Weber ex F.H. Wigg (Asteraceae)

Taraxacum officinale is found in Europe and is a backyard vigorous weed which is having a property to eradicate toxins from the blood and digestive system and also from scavenging free radicals. It is mainly brimming with the varieties of antioxidants and phytonutrients. It also triggers the liver and pancreas to evacuate toxins from the blood stream and detoxify blood (Hu & Kitts, 2003).

Ganoderma lucidum Sheng H. Wu, Y. Cao & Y.C. Dai (Ganodermataceae)

It is a Chinese herb that acts as a tonic, and helps in the detoxification process of the liver. It is rich in phytoconstituents like ganoderic acid which act as antihistamine and lowers the inflammation. Further, it increases the utilization of oxygen in the blood thereby enhancing it. Mushroom is rich in the chemical compounds like triterpenes and ganodosterone having anti-hepatotoxic properties and thus protects the liver from damage. Besides this, patients with acute hepatitis can be cured with this Chinese herb as having a property to regenerate liver cells (Stephlina D'cunha, 2015).

Ocimum basilicum Linn. (Lamiaceae)

Ocimum basilicum is well-known as an antibacterial and anti-inflammatory herb. This African comestible herb has an extraordinary capability to clean or purify the blood and to eliminate any of the toxic substances which is formed in the liver and kidneys. Further, it is magnificent diuretic basil and aids to eradicate toxins from the body through the passage of urine (Singh *et al.,* 2007).

Trifolium pretense Linn. (Fabaceae)

These lilaceous bloom acts as attractive and excellent blood purifiers that cures the deficiencies in the circulatory system. It also lifts up the circulation of blood and prevents the formation of clot by secreting vitamin K. Besides this, herbalists from all over the world used this Red clover for the treatment of cancer and thus well known as an anticancer and antitumor herb (Mueller & Jungbauer, 2008).

Swertia chirata Linn. (Gentianaceae)

From the ancient times, Chirata has been considered as a medicinal herb and used up to treat wide range of human ailments. This herbal plant flourishes in the places of moderate temperatures and grows in the conditions like sandy, loamy and heavy clay soils. Also, it is rich in powerful antioxidants, alkaloids, and glycosides such as stearic acid, oleic acid. It helps in the formation of red blood cells (RBC's). This herb is also an effective remedy for blood purification (Jauhari *et al*., 2017).

Larrea tridentate (D.C.) Covile (Zygophyllaceae)

Larrea tridentate have been used as an anticancer medicine by the Native Americans. In nature, it is considered as a powerful antioxidant and the keystone of most of the anticancer herbal formulas. Nordihydroguaiaretic acid (NGDA) is primary biochemical compound responsible for these antioxidant properties of this herb. NGDA is mainly used as a food preservative or we can say it destroy viruses, bacteria, parasites and other pathogens, hence, also known as anti-pathogenic. *L. tridentate* has even shown great bonding with herpes (Halsey *et al*., 2016). Besides, it cleanses the blood, lymph and urinary tract by eliminating toxins. It also help to inhibit uncontrolled cell proliferation as well as damage to DNA. Many of the recent studies have shown that many tumors or cancers can be treated or dissolved with the help of this medicinal herb (Halsey *et al.,* 2016).

Phytolacca americana Linn. (Phytolaccaeae) and Rumex Crispus Linn. (Polygonaceae)

Both these plants are known for having a property of blood and lymph purification through accelerating the activity of lymph glands in the whole body. Hence, they are known as" blood cleansers". Both of the herbs are fasteners of many anticancer formulas and are used in many traditional herbal medicines (Ahmadi *et al*., 2016).

Mahonia aquifolium (Pursh) Nutt. (Berberidaceae)

Mahonia aquifolium root is bitter in taste and generally used by herbalists as the blood purifier as it has good capacity of stimulation of liver and gall bladder. It cleanses the liver and increases the flow of bile juice, so that the toxic substances may be released out and filter the passage of spleen. Besides, it also helps to metabolize the wastes and toxins of liver. Often natural healers used roots for the treatment of chronic hepatitis-B as it is having the anti-pathogenic properties. Berberine is the main active chemical compound of Oregon grape root that suppresses the growth of different types of tumors or wide variety of neoplastic developments like breast cancer, leukemia, melanoma, and pancreatic cancer, oral and tongue cancers, and prostate cancer (Szeto *et al.,* 2002; Meeran *et al.,* 2008).

Hydrastis canadensis Linn. (Ranunculaceae)

H. canadensis possess various medicinal healing properties and hence is often referred as multifunction herb. One of the characteristic features of this herb is that it cleanses the integral organs of our body and reinforces the immune system. Also, it helps in healthy working of the intestinal system and boost up the functioning of heart, the lymphatic and respiratory system, the liver, the spleen, the pancreas, the colon and various other organs. Berberine is the primary organic compound found in *H. canadensis* root with an antimicrobial property that kills and eradicates various kinds of disease causing organisms like yeast, parasites, bacteria, and even methicillin- resistant *Staphylococcus aureus* (MRSA). It is considered as one of the good blood purifiers and this purification property is because of its capability to eliminate and destroy pathogens from the circulatory cascade of human beings (Hwang *et al.,* 2003).

Rubia cordifolia Linn. (Rubiaceae)

The use of different parts of *R. cordifolia* plant in Ayurveda and Unani medicines dates back to prehistoric times and has long history. It stimulates circulation of

blood and maintains healthy skin. Since this herb cleanses the blood from waste and toxins, it is well known as a model herb in Ayurveda. Moreover, it is also used up as a regulator of immune system (Joharapurkar *et al.,* 2003).

Capsicum annum Linn. (Solanaceae)

This herb is well known for its various important medicinal attributes and its hot fruit, capsicum has been widely used in different remedies for long times. This hot fruit possess a role in increasing the blood circulation and in enhancing the elasticity of the walls of both the arterial and venous systems of circulatory system. Besides, it also plays a major role in managing the normal functioning of blood platelets and maintaining normal blood pressure of the body. The attribute of maintenance of blood pressure by this herb is because of this capsaicin which helps in thinning blood and regulating cholesterol level in body. Many herbalists used this hot fruit as a "driver" to "push" in various herbal formulas as it helps in easy and quick penetration of other herbal remedies into our bloodstream than using them alone. Capsaicin is the main hot compound in this plant which has the ability to activate the signals of apoptosis in cancer cells (Bley *et al.,* 2012; Clark & Lee, 2016).

Tabebuia impetiginosa (Mart. ex DC.) Mattos (Bignoniaceae)

Tabebuia impetiginosa is not herb or shrub, but it is tree that grows well in tropical rain forests. The herbal parts of this tree play an important role in maintaining healthy hepatic system, skin and lymphatic system. It is used as a sour tonic herb to lessen age spots, the side effects of antibiotics, swellings, pain, athlete's foot, blood poisoning, body scent, eczema, fungal contagions and spinal meningitis (Castellanos *et al.,* 2009).

Thinopyrum intermedium (Host) Barkworth and D.R. Dewey (Poaceae)

Thinopyrum intermedium is frequently suggested for the circulatory disorders like low red blood cell count or anemia. Diabetic patients are often fed this herb as it helps to lower the blood glucose level in the body. The juice of this plant is prescribed by many celebrities to take early in mornings as shots and this may help in protecting liver damage or hepatic infections. Many of the studies have been shown that it play a role in protection mechanism by regulating liver and kidney functions, reducing sugar level in blood and also acts as a blood purifier (Marti *et al.,* 2016).

Allium sativum Linn. (Alliaceae)

Since ancient times, garlic is best known for its various medicinal qualities. The fruit of this plant contain higher concentration of sulphur compounds that removes the excess of lipids from the blood. This pungent food is well known as an antibacterial spice and eliminate viruses and pathogens from the body. It also cuts the levels of bad LDL cholesterol and total serum cholesterol. As our body is continuously contaminated day by day by the heavy metals like lead, cadmium, copper etc. from the water and air which enter via food chain and but the level of these metals can be reduced below 19% using garlic, thus garlic helps in reducing toxicity symptoms like headaches, swollen body etc. Thus, garlic may be called as a safer option to clean the body from heavy metals and as a good therapeutic agent (Gebreyohannes & Gerbrechannes, 2013).

Curcuma domestica Linn. (Zingiberaceae)

This plant is worshipped in many cultures and is considered as one of the best "natural healer" and 'golden spice". One of the important assets of the turmeric is that it regulates healthy functioning of hepatic system and has a great power of healing liver and kidney abnormalities. Kidneys and liver are two important organs of human body that serve as centers for cleansing the blood from toxins and impurities and finally detoxifying and eliminating them from body. Further, it has been observed that mixture of turmeric powder and milk has high blood purification power and this healing power can be further extended when this mixture is salted with the ingredients like black pepper, cardamom, cinnamon, clove, and ginger for 72 h. This drink is considered as a good health stimulant and helps the body to regenerate fresh healthy red blood cells with nutrients (David, 1964; Casssileth, 2010).

Acacia catechu (L.f.) Willd. (Fabaceae)

The extract prepared from this natural herb has diverse medicinal characteristics like it acts as an immunomodulator, blood purifier, anodyne, astringent bactericide, refrigerant, detergent, stimulant, styptic, masticatory, expectorant and antiphogistic. It also shows sharp cooling and digestion features, and also acts as good blood purifier. The plant and the extracts prepared from it are used in allergic conditions, colic, diarrhea, and dysentery. It has also been used in treatment and curing of leprosy, ulcers, gum troubles, bronchitis, and anemia and in keeping one away from pathogenic microorganisms due to its anti-helminthic, anti-pyretic, anti-inflammatory properties (Nadumane, 2011; Ghate *et al.,* 2014).

Saccharum officinarum Linn. (Poaceae)

Jaggery popularly known as golden brown unrented sugar is usually produced from *S. officinarum.* This ingredient is attributed with various important medicinal characteristics like it acts as a very potent blood purifier, a good digestive cleaner, prevents constipation, and evacuates waste from the body. Jaggery is rich in micronutrients especially iron, thus it aids in preventing iron deficiencies and reestablish the level of hemoglobin pigment. It also helps to remove blood clots and thus act as a "natural cleaner" of the blood system (Pallavi, 2012).

Citrus limon (Linn.) Osbeck (Rutaceae)

Both in Ayurveda and Naturopathy, lemon drink in warm water is considered best as a good start of the day by medicinal practioners. The lemon juice in warm water acts as good purifier of the blood thus prevents the body from infections. The fibers of lemon help to remove toxin from the digestive tract and thus purify the clean the system (Avello *et al.,* 2014).

Azadirachta indica A. Juss. (Meliaceae)

Azadirachta indica is one the most popular plant and is worshipped by many Hindu people. It is commonly known as "free tree" or "magic tree" in India and found everywhere in India. Various parts of *A. indica* have been found to possess many medicinal benefits to human beings and thus it is highly respected in India. Leaves and roots of this wonderful tree play a great role in circulation and purification of blood and also for the treatment of teeth infections.

In Ayurveda, Unani and Homeopathic medicine, the practice of *A. indica* is enormously well known because it strengthens the enormous array of biologically active compounds, which are chemically varied and structurally composite. Today, more than 140 compounds have been extracted from various parts of this tree like leaves, flowers, seeds, fruits, roots and bark. Traditionally, these parts of plant were used to cure and treat various diseases such as swelling, contagions, fever, skin diseases and dental sicknesses. The leaves of *A. indica* and their constituents have been demonstrated to show immune-modulatory, anti-inflammatory, antioxidant, anti-mutagenic, anti-hyperglycemic, anti-ulcer, antimalarial, antifungal, antibacterial, antiviral, and anti-carcinogenic properties (Bhowmik *et al.,* 2010).

Aloe barbadensis (Linn.) Burm.f. (Asphodelaceae)

Aloe barbadensis is also known as the "lily of desert" is mainly cultivated in Europe and many parts of India. It is one of the best plants used in the traditional medicines. This plant possesses antibacterial and antifungal properties, and thus is used as a good blood purifier. Besides this, it shows anti-inflammatory, fever reliever, spermatogenic, uterine tonic, laxative, purgative and diuretic activities (Singh, 2015). *A. barbadensis* in nature also plays a major role in curing arthritis which is because of the presence of the essential compound anthraquinone and because of this known as anti-arthritis medicine. The plant is also used in preparation of various skin curing medicines and the jelly material obtained from plant is used directly on the skin and hair as good ointment and as good antioxidant (Singh *et al.,* 2015).

Boerhavia diffusa Linn. Nom. Conc. (Nyctaginaceae)

It is a flowering plant commonly called as "punarnava". In terms of Ayurveda, Punarnava means to rejuvenate or renews the body. Basically, the seeds of *B. diffusa* are considered as a promising remedy for the purification of blood. Their seeds are tonic medicine, carminative, useful in backache, scabies and also used as energizer and for keeping healthy digestive system (Bhowmik *et al.,* 2012).

Cichorium intybus Linn. (Asteraceae)

Cichorium intybus is a Mediterranean plant species. It is gaining interests because of its culinary features, nutritional values and medicinal characteristics. *C. intybus* has been functional in traditional medicine and its usage has operated in North Africa and transferred to South Asia for hundreds of years. In Indian drug system, it has been prescribed by doctors to treat fever, diarrhea, spleen expansion, jaundice, enlargement of hepatic system, gout, and rheumatism (Das *et al.,* 2016). The leaves of this plant are first simmered in water followed by addition of sugar in it and taken for appetite loss. The floral parts, especially leaves are cooked as a vegetable and taken regularly for some time for blood purification and to cure body muscular pains and frequent bleeding after child birth (Dar *et al.,* 2018).

Madhuca indica (J. Konig) J.F.Macbr. (Sapotaceae)

It is a type of Indian tropical tree extremely found in the forests and Central and North Indian plains. The flower and seeds of this plant serve as good blood purifiers and thus are used in treating and detoxifying circulatory impurities and toxins (Manjula *et al*., 2013).

Glycyrrhiza glabra Linn. (Fabaceae)

This is widely used medicinal herb in Chinese medicinal system and it shows anti-bacterial properties against *Propionibacterium acnes*, which induces resistance. Various inflammatory mediators are effectively lowered by the phyto-constituents of this plant. This plant also possesses immuno-modulatory activities that help to decrease the cellular immune-competence (Varsha *et al.,* 2013).

Tinospora cordifolia (Thunb.) Miers (Menispermaceae)

This herb is well known for its detoxifying properties and thus enhances cleaning of the blood. Mostly, it eradicates the toxin in the blood circulation and thus boosts up the circulatory system. The use of this herb is mostly suggested and appreciated for those persons who are smokers or alcoholic drinkers (Nadkarni & Nadkarni, 1976; Nayampalli *et al.,* 2007).

Curcuma longa Linn. (Zingiberaceae)

This herb is recognized for its good blood purifying characteristic and also serves as a natural detoxifier, a good carminative, stomachic, appetizer and tonic. Besides it helps in removal and damage of harmful toxins out of the body and thus provides assistance in healing of wounds and allergies (Zahid *et al.,* 2005).

Hemidesmus indicus (Linn.) R.Br. (Apocynaceae)

Traditionally from the Ayurvedic and Modern times, this herb has been known for curative properties as it prevents the skin burn diseases and infections. This herb is also famous for antioxidant, anti-carcinogenic, hepato-protective, antimicrobial, antiacne and many other activities. This herb is known as refreshing coolant as it contains essential oils, tannic acid, tritepenoid, saponins and hemidesmin etc. It is currently used in blood purification as it increases flow of bile juice (Anonymous, 1989).

Smilax china Linn. (Smilacaceae)

It is commonly known as “China root” and it is considered as good blood cleanser, immunomodulator, antimutagenic, detoxifier and tonic. The extract of its root has been used as a remedy in traditional medicines because it helps the body to recover antimicrobial and antimutagenic activities. It increases the viability of cells through the free radical scavenging mechanism (Perera, 2014).

Andrographis paniculata (Burm.f.) Nees (Acanthaceae)

It is commonly called as "green chireta" and it functions as a blood purifier. It is the best remedy to cure for torpid liver and jaundice. In the Ayurvedic medicine preparations, it is used to treat skin diseases. It regulates hepatic and kidney functions and prevents skin disorders by the process of detoxification. This plant has been extensively used as antimicrobial agents that show the influential antibacterial, antiviral, antihelminthic (against *Ascaris lumbricoides*), and antimalarial activities (Singh *et al.,* 2003; Parichatikanond *et al.,* 2010).

Psoralea corylifolia Linn. (Fabaceae)

It is an erect high annual herb found throughout India, mainly in Uttar Pradesh, Bengal and Maharashtra. Every part of this plant like root, stem and leaves has its own values (Chauhan, 2013). The extract or powdered form of *P. corylifolia* is useful to treat blood problems and skin disorders like leukoderma, skin rashes etc. (Lee *et al.,* 2019).

Berberis aristata DC. (Berbaridaceae)

It is commonly known as "tree turmeric" and "Indian barberry". Juicy fruit of this herb contains plenty of sugars, and is rich in vitamin-C and other nutrients. This plant helps in healing of wounds, skin disease, eye infections, jaundice, diarrhea and blood purification. Pharmacological studies have shown that it relaxes the circulatory system and also possess antioxidant, antibacterial, antifungal, antipyretic, anti-inflammatory and hepato-protective features (Chauhan, 2013).

Ocimum sanctum Linn. (Lamiaceae)

Tulsi is holy basil, an aromatic perennial plant widely used to cure many diseases. Extracts of tulsi leaves are used to manage the skin disorders, anti-stress and anti-oxidant immunomodulators. The linoleic acid lipooxygenase cascade is responsible for the anti-inflammation activities and circulation of blood (Singh *et al.,* 2007).

Emblica officinalis Linn. (Phyllanthaceae)

In Indian traditional medicinal system, *E. officinalis* is considered as the most important medicinal plant. Various parts of this plant are used to treat number of human infections and diseases, but among these different parts, the fruit is the most widely used remedy. It is used either alone or in combination with others in treating

various diseases and bears innumerable health benefits. The fruits of this plant are considered as the richest source of vitamin C (Ascorbic acid) up to 445 mg per 100 gm. They also contain the pigment, antioxidant polyphenols, and vitamins A and B. They function as anti-aging and anticancer drugs and fight in inflammation and neurological disorders.

Traditionally, it plays a major role in purification of the blood, treatment of cough and fever as it is rich in iron and many other beneficial nutrients. It is often recommended to the patients suffering from diabetes, cardiac and eyes disorders (Mohanapriya & Ramaswamy, 2012). Besides, it relieves constipation and is used for enhancing digestive system. A fixed oil of this plant is mainly used for strengthening hair follicles and improving the growth of hairs. Dried fruit is used as an ingredient of shampoo and hair oil with a property of hair hygiene (Nadkarni & Nadkarni, 1999).

CONCLUSION

Since from the ancient times, herbal plants and medicines have been widely used by the doctors and patients for their better therapeutic values. As these herbs and medicines prepared from them do not have any adverse or side effects as compared to the modern medicines, it has been used extensively all over the world. The medicines prepared in ayurvedic and unani system can be utilized in a better form with enhanced efficacy by incorporating them in modern dosage forms. However, pharmacologists need a scientific approach to deliver the components in a novel manner to build up patient compliance and circumvent frequent administration. This can be obtained by preparing novel drug delivery systems for herbal constituents. The various plant products can be investigated for their medicinal properties, especially their role in circulatory system activities and in blood purification, thus enabling the body to reduce the toxic wastes either through neutralization or by the elimination. Such type of medicinal blood purifier plants may or may not be accompanied with other medicinal plants. In conclusion, the blood purifiers produces a least laxative effect and at the same time enhance the immune system of the body.

REFERENCES

Abdullahi, A. A. (2011). Trends and challenges of traditional medicine in Africa. *African Journal of Traditional, Complementary, and Alternative Medicines*, *8*(5S), 115–123. doi:10.4314/ajtcam.v8i5S.5 PMID:22754064

Ahmadi, B. B., Bahmani, M., Eftekhari, Z., Jelodari, M., & Mirhoseini, M. (2016). Overview of medicinal plants used for cardiovascular system disorders and diseases in ethnobotany of different areas in Iran. *Journal of Herbmed Pharmacology*, *5*, 39–44.

Alves, R. R., & Rosa, I. M. (2007). Biodiversity, traditional medicine and public health: Where do they meet? *Journal of Ethnobiology and Ethnomedicine*, *3*(1), 3. doi:10.1186/1746-4269-3-14 PMID:17376227

Anonymous. (1989). The Ayurvedic Pharmacopoeia of India. Ministry of Health and Family Welfare, Department of Health, Govt. of India.

Avello, M., Jofre, P., Pastene, E., & Fernandez, P. (2014). Use of *Citrus limon* L. (lemon) in treating blood pressure sudden rises. *International Journal of Pharmacognosy and Phytochemical Research*, *6*(3), 606–611.

Bhowmik, D., Chiranjib, Y. J., Tripathi, K. K., & Kumar, K. P. S. (2010). Herbal remedies of *Azadirachta indica* and its medicinal application. *Journal of Chemical and Pharmaceutical Research*, *2*(1), 62–72.

Bhowmik, D., Kumar, K. P. S., Srivastava, S., Paswan, S., Sankar, A., & Dutta, D. (2012). Traditional indian herbs punarnava and its medicinal importance. *Journal of Pharmacognosy and Phytochemistry*, *1*, 52–57.

Bley, K. B., Boorman, G., Mohammad, B., McKenzie, D., & Babbar, S. A. (2012). Comprehensive review of the carcinogenic and anti-carcinogenic potential of *Capsaicin*. *Toxicologic Pathology*, *40*(6), 847–873. doi:10.1177/0192623312444471 PMID:22563012

Boakye, M. K., Pietersen, D. W., Kotzé, A., Dalton, D. L., & Jansen, R. (2015). Knowledge and uses of African pangolins as a source of traditional medicine in Ghana. *PLoS One*, *10*(1), e0117199. doi:10.1371/journal.pone.0117199 PMID:25602281

Boehme, J. (1982). *Signature of all things*. Cambridge: James Clarke & Co.

Cassileth, B. (2010). Turmeric (*Curcuma longa, Curcuma domestica*). *Oncology*, *24*(6). PMID:20568597

Castellanos, G. J. R., Prieto, J. M., & Heinrich, M. (2009). Red Lapacho (*Tabebuia impetiginosa*)-a global ethnopharmacological commodity? *Journal of Ethnopharmacology*, *121*(1), 1–13. doi:10.1016/j.jep.2008.10.004 PMID:18992801

Chauhan, S. (2013). An overview on blood purifier. *International Research Journal of Pharmacy*, *4*(9), 8–10. doi:10.7897/2230-8407.04903

Chopra, A. (2000). Ayurvedic Medicine and Arthritis. *Rheumatic Disease Clinics*, *26*(1), 133–144. doi:10.1016/S0889-857X(05)70127-7 PMID:10680201

Clark, R., & Lee, S. (2016). Anticancer properties of *Capsaicin* against human cancer. *Anticancer Research*, *36*, 837–844. PMID:26976969

D'cunha. (2015). *Purify your blood naturally with these five Herbs*. Academic Press.

Dar, M. S., Joo, N., & Ganaie, S. A. (2018). Medicinal plants used by tribal and rural community of Sata Pokhran area of tehsil Pampore of district Pulwama, Jammu and Kashmir-India. *Journal of Phytopharmacology*, *7*(1), 66–71.

Das, S., Vasudeva, N., & Sharma, S. (2016). *Cichorium intybus*: A concise report on its ethnomedicinal, botanical and phytopharmacological aspects. *Drug Design, Development and Therapy*, *7*(1), 1–12. doi:10.4103/2394-6555.180157

David, E. S. (1964). Indigenous uses of turmeric (*Curcuma domestica*) in Asia and Oceania. *ANTHROPOS: International Review of Anthropology and Linguistics*, *59*, 93–127.

Dobos, G. J., Tan, L., Cohen, M. H., McIntyre, M., Bauer, R., Li, X., & Bensoussan, A. (2005). Are national quality standards for traditional Chinese herbal medicine sufficient? Current governmental regulations for traditional Chinese herbal medicine in certain Western countries and China as the Eastern origin country. *Complementary Therapies in Medicine*, *13*(3), 183–190. doi:10.1016/j.ctim.2005.06.004 PMID:16150372

Dong, J. C. (2013). The Relationship between Traditional Chinese Medicine and Modern Medicine. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–10. doi:10.1155/2013/153148 PMID:23983772

Fabricant, D. S., & Farnsworth, N. R. (2001). The value of plants used in traditional medicine for drug Discovery. *Environmental Health Perspectives*, *109*, 69–75. PMID:11250806

Gebreyohannes, G., & Gebreyohannes, M. (2013). Medicinal values of garlic: A review. *International Journal of Medical Sciences*, *5*(9), 401–408.

Ghate, N. B., Hazra, B., Sarkar, R., & Mandal, N. (2014). Heartwood extract of *Acacia catechu* induces apoptosis in human breast carcinoma by altering bax/bcl-2 ratio. *Pharmacognosy Magazine*, *10*(37), 27–33. doi:10.4103/0973-1296.126654 PMID:24695415

Gurib-Fakim, A. (2006). Medicinal plants: Tradition of yesterday and drugs of tomorrow. Review article. *Molecular Aspects of Medicine*, *27*(1), 1–93. doi:10.1016/j.mam.2005.07.008 PMID:16105678

Halsey, R.W. & Keeley, J.E. (2016). *Conservation Issues: California Chaparral*. Academic Press.

Holtz, C. (2007). *Global health care: Issues and policies*. Sudbury, MA: Jones & Barlett Publishers.

Hu, C., & Kitts, D. D. (2003). Antioxidant, pro-oxidant and cytotoxic activities of solvent fractionated dandelion (*Taraxacum officinale*) flower extracts in vitro. *Journal of Agricultural and Food Chemistry*, *51*(1), 301–310. doi:10.1021/jf0258858 PMID:12502425

Hwang, B. Y., Roberts, S. K., Chadwick, L., Wu, C. D., & Kinghorn, D. A. (2003). Antimicrobial constitutents from goldenseal (the rhizomes of *Hydrastis canadensis*) against selected oral pathogens. *Planta Medica*, *69*(7), 623–627. doi:10.1055-2003-41115 PMID:12898417

Imperato, P. J. (1981). Modern and traditional medicine: The case of Mali. *Annals of Internal Medicine*, *95*(5), 650–651. doi:10.7326/0003-4819-95-5-650 PMID:7294557

Jauhari, N., Bharadvaja, N., & Sharma, N. (2017). *Swertia chirata*: A comprehensive review with recent advances. *Current Pharmaceutical Biotechnology*, *18*(9), 730–739. doi:10.2174/1389201018666171026153515 PMID:29076426

Joharapurkar, A. A., Zambad, S. P., Wanjari, M. M., & Umathe, S. N. (2003). *In vivo* evaluation of antioxidant activity of ethanolic extract of *Rubia cordifolia* Linn.and its influence on ethanol-induced immunosuppression. *Indian Journal of Pharmacology*, *35*, 232–236.

Kapoor, L. D. (1990). *CRC Handbook of Ayurvedic medicinal plants*. Boca Raton, FL: CRC Press.

Kaur, A., Nain, P., & Nain, J. (2012). Herbal plants used in treatment of Rheumatoid arthritis: A review. *International Journal of Pharma Sciences*, *4*(4), 44–57.

Lev, E. (2006). Ethno-diversity within current ethno-pharmacology as part of Israeli traditional medicine–A review. *Journal of Ethnobiology and Ethnomedicine*, *2*(1), 4. doi:10.1186/1746-4269-2-4 PMID:16401348

Li, A., Gao, M., Zhao, N., Li, P., Zhu, J., & Li, W. (2019). Acute liver failure associated with Fructus Psoraleae: A case report and literature review. *BMC Complementary and Alternative Medicine*, *19*(1), 1–4. doi:10.118612906-019-2493-9 PMID:30975110

Lone, A. H., Ahmad, T., Anwar, M., Sofi, G., Imam, H., & Habib, S. (2012). Perception of health promotion in Unani herbal medicine. *Journal of Herbal Medicine*, *2*(1), 1–5. doi:10.1016/j.hermed.2012.02.003

Lu, M. (2013). Status and trends of chinese traditional medicine industry. Chin. *Indian Journal of Pharmaceutical Sciences*, *44*, 214–216.

Magner, L. N. (1992). *A history of medicine*. New York: Marcel Dekker Inc.

Manjula, S., & Mamidala, E. (2013). An ethnobotanical survey of medicinal plants used by traditional healers of Thadvai, Warangal district, Andhra Pradesh, India. *International Journal of Medical Research and Health Sciences*, *2*(1), 40–46.

Marti, A., Bock, J. E., Pagani, M. A., Ismail, B., & Seetharaman, K. (2016). Structural characterization of proteins in wheat flour doughs enriched with intermediate wheatgrass (*Thinopyrum intermedium*) flour. *Food Chemistry*, *194*, 994–1002. doi:10.1016/j.foodchem.2015.08.082 PMID:26471645

Meeran, S. M., Katiyar, S., & Katiyar, S. K. (2008). Berberine-induced apoptosis in human prostate cancer cells is initiated by reactive oxygen species generation. *Toxicology and Applied Pharmacology*, *229*(1), 33–43. doi:10.1016/j.taap.2007.12.027 PMID:18275980

Mogami, S., & Hattori, T. (2014). Beneficial effects of rikkunshito, a Japanese kampo medicine, on gastrointestinal dysfunction and anorexia in combination with Western drug: A systematic review. *Evidence-Based Complementary and Alternative Medicine*. doi:10.1155/2014/519035 PMID:24778703

Mohanapriya, M. & Ramaswamy, L. (2012). Amla- the wonder of ayurvedic medicine. *Journal of Ayurvedic and Herbal Medicine*, *2*(5), 828-834.

Mueller, M., & Jungbauer, A. (2008). Red clover extract: A putative source for simultaneous treatment of menopausal disorders and the metabolic syndrome. *Menopause (New York, N.Y.)*, *15*(6), 1120–1131. doi:10.1097/gme.0b013e31817062ce PMID:18724264

Nadkarni, K. M., & Nadkarni, A. K. (1976). *Indian Meteria Medica* (3rd ed., Vol. 1). Popular Prakasan Pvt. Ltd Mumbai.

Nadkarni, K. M., & Nadkarni, A. K. (1999). *Indian materia medica - with ayurvedic, unani-tibbi, siddha, allopathic, homeopathic, naturopathic and home remedies* (Vol. 1). Bombay, India: Popular Prakashan Private Ltd.

Nadumane, V. K. (2011). Evaluation of the anticancer and cytotoxic potentials of *Acacia catechu* extracts in vitro. *The Journal of Pharmacy and Pharmacology*, *2*, 190–195.

Nayampalli, S., Ainapure, S. S., & Nadkami, P. M. (1982). Study of antiallergic acid bronchodilator effect of *Tinospora cordifolia. Indian Journal of Pharmaceutical Sciences*, *14*, 64–66.

Oliver, S. J. (2013). The role of traditional medicine practice in primary health care within Aboriginal Australia: A review of the literature. *Journal of Ethnobiology and Ethnomedicine*, *9*(1), 9. doi:10.1186/1746-4269-9-46 PMID:23819729

Padua de, L.S., Bunyapraphatsara, N., & Lemmens, R.H.M.J. (1999). Plant resources of South-East Asia, No 12(1). Medicinal and Poisonous Plant 1. Backhuys Publishers.

Pallavi, R., Elakkiya, S., Tennety, S. S. R., & Devi, P. S. (2012). Anthocyanin analysis and its anticancer property from sugar cane (*Saccharum officinarum*) peel. *International Journal of Research in Pharmacy and Chemistry*, *2*(2), 338–345.

Parasuraman, S., Thing, G. S., & Dhanaraj, S. A. (2014). Polyherbal formation: Concept of Ayurveda. *Pharmacognosy Reviews*, *8*(16), 73–80. doi:10.4103/0973-7847.134229 PMID:25125878

Parichatikanond, W., Suthisisang, C., Dhepakson, P., & Herunsalee, A. (2010). Study of anti-inflammatory activities of the pure compounds from *Andrographis paniculata* (Burm.f.) Nees and their effects on gene expression. *International Immunopharmacology*, *10*(11), 1361–1373. doi:10.1016/j.intimp.2010.08.002 PMID:20728594

Patwardhan, B., Warude, D., Pushpangadan, P., & Bhatt, N. (2005). Ayurveda and traditional Chinese medicine: A comparative overview. *Evidence-Based Complementary and Alternative Medicine*, *2*(4), 465–473. doi:10.1093/ecam/neh140 PMID:16322803

Perera, B.P.R. (2014). A study on the plants used as Chopachini. *Journal of Homeopathy and Ayurvedic Medicine*, *3*, 170.

Qi, F. H., Wang, Z. X., Cai, P. P., Zhao, L., Gao, J. J., Kokudo, N., ... Tang, W. (2013). Traditional Chinese medicine and related active compounds: A review of their role on hepatitis B virus infection. *Journal of Drug Discovery and Therapeutics*, *7*, 212–224. PMID:24423652

Shi, Q. W., Li, L. G., Huo, C. H., Zhang, M. L., & Wang, Y. F. (2010). Study on natural medicinal chemistry and new drug development. *Chinese Traditional and Herbal Drugs*, *41*, 1583–1589.

Singh, P. K., Roy, S., & Dey, S. (2003). Antimicrobial activity of *Andrographis paniculata. Fitoterapia*, *74*(7-8), 692–694. doi:10.1016/S0367-326X(03)00159-X PMID:14630176

Singh, R. (2015). Medicinal plants: A review. *Journal of Plant Sciences*, *3*, 50–55.

Singh, S., Taneja, M., & Majumdar, D. K. (2007). Biological activities of *Ocimum sanctum* L. fixed oil- An overview. *Indian Journal of Experimental Biology*, *45*, 403–412. PMID:17569280

Szeto, S., Yow, C. M. N., & Fung, K. W. (2002). Characterization of berberine on human cancer cells in culture. *Turkish Journal of Medical Sciences*, *32*, 363–368.

Varsha, S., Agrawal, R. C., & Sonam, P. (2013). Phytochemical screening and determination of anti-bacterial and anti-oxidant potential of *Glycyrrhiza glabra* root extracts. *Journal of Environmental Research and Development*, *7*(4), 1552–1558.

Watanabe, S., Imanishi, J., Satoh, M., & Ozasa, K. (2001). Unique place of Kampo (Japanese traditional medicine) in complementary and alternative medicine: A survey of doctors belonging to the regional medical association in Japan. *The Tohoku Journal of Experimental Medicine*, *194*(1), 55–63. doi:10.1620/tjem.194.55 PMID:11556734

World Health Organization. (2000). *General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine*. Geneva, Switzerland: World Health Organization.

Yakubo, S., Ito, M., Ueda, Y., Okamoto, H., Kimura, Y., Amano, Y., ... Watanabe, K. (2014). Pattern classification in kampo medicine. *Evidence-Based Complementary and Alternative Medicine*, 2014. PMID:24701241

Yu, F., Takahashi, T., Moriya, J., Kawaura, K., Yamakawa, J., Kusaka, K., ... Kanda, T. (2006). Traditional Chinese medicine and Kampo: A review from the distant past for the future. *The Journal of International Medical Research*, *34*(3), 231–239. doi:10.1177/147323000603400301 PMID:16866016

Zahid, A. M., Hussain, M. E., & Fahim, M. (2005). Antiatherosclerotic effects of dietary supplementations of garlic and turmeric: Restoration of endothelial function in rats. *Life Sciences*, *77*(8), 837–857. doi:10.1016/j.lfs.2004.11.039 PMID:15964306

Zhang, A. H., Sun, H., Qiu, S., & Wang, X. J. (2013). Advancing drug discovery and development from active constituents of yinchenhao tang, a famous traditional Chinese medicine formula. *Evidence-Based Complementary and Alternative Medicine*. doi:10.1155/2013/257909 PMID:24191164

Chapter 2
Antidiabetic Activity (Anti-Hyperglycemic Activity, Anti-Hyperlipidemic Activity)/ Agents From Medicinal Plants

Manish Singh Sansi
National Dairy Research Institute, India

Daraksha Iram
National Dairy Research Institute, India

Kapil Singh Narayan
National Dairy Research Institute, India

Sandeep Kumar
https://orcid.org/0000-0002-7576-9696
National Dairy Research Institute, India

Om Prakash
National Dairy Research Institute, India

Dipanjan Misra
National Dairy Research Institute, India

ABSTRACT

Diabetes mellitus (DM) is a chronic disease caused by inherited or acquired deficiency in insulin secretion and by decreased insulin secretion by the organ. Insulin deficiency causes the DM. Synthetic drugs are widely used in the treatment of diabetes, but they have some side effects. The antihyperglycemic and antihyperlipedemic effects

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of the plants are related to their ability to maintain pancreatic function. Medicinal plants constituents such as glycosides, alkaloids, terpenoids, and flavonoids mitigate DM. B. ciliata inhibits the α-glucosidase and α-amylase. Cinnamon extracts improve insulin receptor function by activating insulin receptor kinase and inhibiting insulin receptor phosphatase, which lead to an increase in insulin sensitivity. Morinda lucida also had the highest antioxidant activity, and it also inhibited the α-glucosidase. Many plants have also been shown to antihyperlipedemic effects. Finally, it can be concluded that medicinal plants have that ability to treat or prevent DM.

INTRODUCTION

Diabetes is the metabolic disease of carbohydrates, proteins and fats, and a prolonged disease that increases when the pancreas is not able in a function to synthesize insulin, or the physique can't create perfect use of the insulin it produces (Kooti *et al.,* 2016). Insulin is the hormone which is the synthesized by the pancreas that functions as a key to transport glucose from the foods into the cells to release energy for body functions. All the carbohydrate ingredients are breakdown into glucose in the blood. Insulin also helps to glucose get into the cells (Kumar *et al.,* 2011). Diabetes mellitus is not now a disease alternatively is the a group of metabolic disorders characterised by way of prolonged hyperglycemia, succeeding from failings in the secretion of insulin, increase thirst, extend ketonuria and ketonemia, urinary output are the collective signs of DM (Andrade-Cetto & Wiedenfeld, 2004). The estimated range of the diabetic patients 171 million globally in the 2000 is likely to be expand at least 366 million till the year 2030 (Shinde *et al.,* 2014). Over the long-standing high level of glucose are associated with injury to the physique and the failure of a tissues and organs. Though there are the range of procedures to decrease the patients of diabetes and its secondary complications, many desired natural formulation are there to reduce the cost.

Types of DM

The β-cell imperfections and the insulin resistance in the pancreas lead to the progress of 4 main types of DM.

Type-1 Diabetes

This is now denoted that, the (IDDM) Insulin dependent diabetes mellitus or the immune-mediated diabetes. In this case very little or no insulin produced. It is reason with the aid of autoimmune response which assaults the insulin-producing β-cells (Nazarian-Samani *et al.,* 2018). This is hardly brought about due to mutation in the HLA the chromosome locus is 6p21 generally known as IDDM1 (Ali *et al.,* 2006). Type-1 diabetes can have an effect on people at whichever age, however generally develops in the children or adults, young peoples. This type of diabetes the patients want injections of insulin daily to control the blood glucose levels (Shori, 2015).

These are most common a symptom of the type-1 diabetes includes: increase the dry mouth and thirsting; sudden weight loss; regular of urination; tiredness and Lack of the energy; continual hunger, unclear of the vision

Type-2 Diabetes

The Type-2 diabetes is the moreover known as the Non-Insulin Dependent Diabetes Mellitus (NIDDM). It is shows, that insulin resistance and low insulin excretion and debts, ~90% of situations of the type-2 diabetes. T2D generally takes region later the age of 40 years, The T2D is the most prevalent types of diabetes, and the numbers of the mostly ~90% of all the diabetes cases. Because the insulin can't work properly, and the blood glucose ranges keep rising, and releasing extra insulin (Apostolidis *et al.,*2007). The many risk factors have been related with the type-2 diabetes and include: family history of the diabetes; overweight, harmful diets; physical indolence; increasing the age; increase blood pressure; impaired glucose tolerance (IGT); reduced nutrition during the pregnancy. The signs of type-2 diabetes are alike to those of type-1 diabetes are includes: dry mouth and excessive thirst; regular urination; tiredness and lack of energy; low healing wounds; unclear vision

Hyperglycemia or Hyperglycaemia

The occurrence of diabetes is the increasing, specifically growing in newly industrial countries. Approximately ninety per cent of all instances of diabetes in the growing and developed countries are noninsulin-dependent diabetes mellitus, additionally observed as type-2 diabetes (T2D) (Di Carli *et al.,* 2003). These establishes are generally in adults of greater than 30 years of the age and are often characterised with the resource of postprandial hyperglycemia. The prevalence of excessive blood glucose (hyperglycaemia) in being pregnant will extend unexpectedly with age and is the best possible in female over the age of forty five years (Manukumar *et al.,* 2017).

The Short-terms symptoms of the excessive blood sugar include are: unnecessary of thirst; excessive of urination; increase urination at the night; blurred vision; fatigue.

Resistance of Insulin

In the case of insulin resistance (IR) the body cells do not longer use insulin however the glucose of blood requires high insulin to transport the blood glucose into cells (Rahier *et al.,* 2008). Still, this is not the clear that, it is from insulin deficiency or the IR. The obesity is the sustained to be one of the predominant elements inflicting to enhance T2D (Gushiken *et al.,* 2016).

Genetic Background

On the research Based numerous genes have been diagnosed which are involved in T2D. The prevalence of IR, interplay of insulin with Insulin Specific Receptor (INSR) on insulin responsive cell surface is vital (Taika *et al.,* 2018). Pathophysiology of insulin action in the body structured on the INSR activation, accompanied by using skill of activation of precise the transduction of signaling. If there are imperfections in the INSR gene, there is the possibility of growing T2D (Manukumar *et al.,* 2017). This genes mutation occurs in completely 3-4% sufferers with a genetic irregularity in the receptor protein, predominant to the disorder.

The Gestational Diabetes Mellitus

The GDM (Gestational diabetes mellitus) is each different kind of diabetes; show up in the path of being pregnant due to excessive blood glucose levels. Gestational diabetes is mainly described as glucose intolerance with start or first focal point at some point of being pregnant and completely weight-reduction plan variation is used to treat with the GDM (Crowther *et al.,* 2005). During the 2005, the one group commenced the research trials of the ACHOIS (Australian Carbohydrate Intolerance Study) on the Pregnant Women to set up the GDM and the issues correlated (Bantle *et al.,* 2008). Outcome of ACHOIS referred to that, meals routine programmed recover the GDM linked woman's health with incredible of existence.

The Secondary Diabetes

The SD (Secondary diabetes) takes region due to the genetic defects in the β-cell characteristic however in which the glucose levels is controlled by way of potential of profitable iron depletion. SD is a situation lead via capacity of some conditions such as, pancreatectomy, glucagonoma, Hemochromatosis, the Chronic pancreatitis

etc. and it is requires insulin injection to preserve the sugar of blood and stage beneath manipulate (Lipinski *et al.,* 2001). It's challenging for human beings who had pancreatectomy to the produce personal insulin. Therefore, the ordinary insulin injection is wished to control Secondary diabetes as like T1D. Since historical times, the raw plants and their extracts are used to combat diabetes (Raskin *et al.,* 1995).

ANTIDIABETIC MEDICINAL PLANT MECHANISM

There are numerous vital modes of the action for natural products in diabetes mellitus. The most essential mechanisms include that the act through way of the stimulating insulin secretion, α-glucosidase, and inhibiting α- amylase (Nasri, 2013), augmenting the PPARs, (peroxisome proliferator-activated receptors) and inhibiting the secretion of the incretion, free radical scavenging plus antioxidant interest (against reactive oxygen or nitrogen species (ROS/ RNS)), GLP-1, inhibiting advanced glycation end-product (AGE) formation, the up-regulating or elevating translocation of the glucose transporter which kind four (GLUT-4), and stopping improvement of the insulin resistance (Nazarian-Samani *et al.,* 2018).

Insulin Secretagogues

The some plants or their parts stimulate the secretion of insulin i.e. *Trigonella foenum-graecum* Linn. (Fabaceae). This additionally will increase the glucose metabolism not solely by using stimulating the adipocyte differentiation but also through the reduction of infection in adipocytes and also increase the expression of peroxisome proliferator-activated receptors. In *Momordica charantia* Linn. (Cucurbitaceae) 9-cis, 11-trans, and 13-trans-conjugated linolenic has been observed to activate PPAR-α in rat tissues (Chuang *et al.,* 2006). The limonoids azadiradione and gedunin plus and the tetranortriterpenoid compound meliacinolin isolated from *A. indica,* these are the additionally inhibitory on both α-amylase and α-glucosidase enzymes in a similar way indicating that these medicinal plant has a tendency to decrease the post-prandial hyperglycemia in the diabetic circumstance (Sudha *et al.,* 2011). So, the minimize rate of the glucose absorption and a subsequent reduction in the rate of increase of postprandial blood glucose (Perez-Gutierrez & Daian-Gugman, 2012). The many synthetic inhibitors or anti-diabetic agents, such as miglitol and voglibose, acarbose, it can also decrease the absorption rate of glucose via slowing down carbohydrate digestion, causing a decrease in postprandial serum glucose level.

Increased the Glucagon-Like Peptide-1 Secretion

The saponin is (ginsenosides) found in *P.ginseng* which stimulate the GLP-1 secretion, and this incretion reduces the hyperglycemia significantly contributing to an anti-diabetic effect (Liu *et al.,* 2014). The Catalpol compound isolate from *Rehmannia glutinosa* of restrains AGE-mediated the infection by using inhibiting the ROS production and also the NADPH-oxidase activity, and this is significant to prevent AGE-mediated risk in DM.

Free Radical Scavenging Activity

The *T. foenum-graecum* seeds must extend antioxidant activity in the blood which is suggesting that disconcerted free radical metabolism in the diabetic situation may also additionally be decrease back to every day (Dzib-Guerra *et al.,* 2016). The plants extract from *R. glutinosa* rhizome displayed the free radical scavenging recreation decreasing the degree of ROS intracellular in accumulation to decrease of the pro-inflammatory gene expression, and this discovering has been promoted as a therapeutic possibility for the DM disease.

Up-Regulation and Translocation Transporter of Glucose Type-4

The Glut-4 enzyme is the best insulin delimited glucose transporters which is positioned at the surface membrane of the cardiac muscle cells, skeletal muscle cells and adipocytes. The triterpenoids ingredient of cucurbitane and *M. charantia* fruits stimulates the cell membrane translocation of GLUT-4 to enable the AMPK phosphorylation and uptake of glucose (Cao *et al.,* 2007). The extract of the Cinnamon conjures up a biphasic action on the GLUT-4 mRNA, while is an active constituent of the plant that is cinnamaldehyde compound increases the glucose uptake via increased translocation of GLUT-4.

Insulin Resistance Reduction (IR)

The IR is an uncontrolled disorder in which cells do not respond to the insulin hormone (Chattopadhyay *et al.,* 1993). Similarly, the meliacinolin compound isolated from the leaves of *A. indica* which inhibits IR and it has the wide-ranging of other anti-diabetic modes of action.

Hyperlipidemia

Hyperlipidemia is a disease initiated by increase in the level of lipids in the plasma comprising cholesterol esters, TG, cholesterol, VLDL, LDL and also it comprising reduce the levels of HDL in the plasma (Mishra *et al.,* 2011). This increasing lipids abnormality finally leads to the type-1 and type-2 DM. The Lipids abnormality in type-1 DM is directly associated to bad glycemic control which is the most frequent abnormality is hypertriglyceridemia (Crulckshanks *et al.,* 1985). Hypertriglyceridemia is an important kind of hyperlipidaemia triggered by lack of ability of the body to clear VLDL and chylomicrons by the decrease in the lipoprotein lipase activity (Ginghina *et al.,* 2011).

Types of Hyperlipidemia

Hyperlipidemic conditions generally classified into two main categories:

Primary

This kind of hyperlipidemia is due to genetic defect therefore this is also known as familial. It may additionally be monogenic and a single gene defects or the polygenic, and multiple gene defects. The Primary hyperlipidemia can normally be fixed into one of the abnormal lipoprotein patterns at early stage (Tripathi et al., 2008).

Secondary

This kind of hyperlipidemia is due to acquired modifications due to the fact it is induced by means of any other disorders such as nephritic syndrome, diabetes, continual alcoholism, and hypothyroidism beside this used of excess drugs like oral contraceptives and β- blockers, corticosteroids. The Secondary hyperlipidemia collectively with the important hypertriglyceridemia can causes pancreatitis (Kumar *et al.,* 2012).

Drugs Available for Hyperlipidemia Treatment

LDL and cholesterol are the fundamental atherogeniclipo protein and the reduction of these lipids molecules would be anticipated to reduce the atherosclerosis. However decreased cardiovascular adverse effects had been observed with low LDL and cholesterol (Wouters *et al.,* 2005). In treatment of hyperlipidemia monotherapy has been shown to be the highly effective therapy. But the completion of whole approach combination of medication may also be essential. Presently, the antihyperlipidemic

drugs comprise statins, and fabric acid derivative, derivatives of nicotinic acid and resins of bile acid binding, and also the drugs that inhibits the absorption of cholesterol (Joseph, 2011).

Plant Products to Treat the Hyperlipidemia

The side effects and high cost of artificial drugs, various plant products have grown to be the finest substitute approach as the harmless and antilipidemic drugs. Numbers of the plant species have been acknowledged and mentioned with hypolipidermic properties and used as natural products in the current remedy for hyperlipidemia. Numerous herbal plants, their crude and isolated factors discovered from many plants, which are superb medicines for hyperlipidemia patients. Polyphenols as genistein, apigenin and catechins alongside with sterols, saponins, stanols, mucilage, polyunsaturated fatty acids are examples of the dealers discovered in plant and showcase hypocholesterolemic effect.

Fagopyrum Esculentum Moench (Polygonaceae)

It is an Asian plant generally called as Japanese buckwheat or buckwheat having to anti-obesity and antidiabetic property (Son *et al.,* 2008; Kawa *et al.,* 2003). Extract of this plant have capability to minimize triglycerides (TG) and it is help to the elimination of acid sterol acid and intestinal bile (Tomotake *et al.,* 2006). The bran extract of this plant especially down regulate the gene expression of lipogenic enzymes such as stearyl CoA desaturase-1, FAS and acetyl CoA oxidase. Furfure glucose converted into acetyl-CoA then acetyl-CoA is the source of triglycerides synthesis, so buckwheat have glucose reducing have an impact on which is associated to decreasing triglycerides (Postic *et al.,* 2004). Therefore, extra uptake of glucose triggers lipogenesis genes, which are fatty acid synthase and acetyl-CoA carboxylase then due to this fact buckwheat bran extract have capable to limit glucose, and decrease TG (Andreolas *et al.,* 2002).

Nigella Sativa Linn. (Ranunculaceae)

In Indian traditional system of medicine it is used in dyslipidemia. Thymoquinone (TQ) is energetic compound of *N. sativa* which is 30 to 48% constituents present in the black seeds that is responsible for the maximum plant properties. TQ inhibits the hepatic HMGR or HMG-CoA reductase enzyme. Its effect rises level of arylesterase, and moreover alter the genes that stimulate cholesterol metabolism. TQ moreover possess antioxidant property that consequences (Amin & Hosseinzadeh, 2016).

Allium Sativum Linn. (Alliaceae)

It is used for prevention of excessive triglycerides, LDL cholesterol and atherosclerosis (Putri *et al.,* 2017). Boiled extract of garlic once no longer decrease the triglycerides due to the fact of destruction of active volatile, and the chemically not stable elements in boiled extracts however its raw extract decreasing LDL cholesterol (Thomson *et al.,* 2006). It contains the active organosulfur compounds such as diallyl-disulfide, allyl cysteine, γ-glutamyl-S-methyl cysteine, S-propyl cysteine (SPC), S-ethyl cysteine (SEC), and S-allyl cysteine (SAC) are soluble in water that facilitated the inhibition of mono oxygenase and FAS. Acetate incorporation into fatty acid synthesis reduce via these compounds which lead to the disruption of TG synthesis (Liu & Yeh 2001). Garlic ingrediants moreover inhibit the FAS and also inhibit the glucose-6 phosphate dehydrogenase (G6PD), which are mediator in LDL cholesterol and TG synthesis (Ashraf *et al.,* 2011).

Curcuma Longa Linn. (Zingiberaceae)

Curcumin is the major constituents used as immunomodulator in way of life and Ayurveda since centuries (Mollazadeh *et al.,* 2019). *C. longa* inhibits the low density lipid (LDL) oxidation (Ramırez-Tortosa *et al.,* 1999). It confirmed the hypolipidemic effect, and additionally it extended the serum HDL stage in animal research (Arafa *et al.,* 2005). Cholesterol absorption in Intestine inhibit via the curcumin. Cholesterol-7α-hydroxylase is associated with bile acid biosynthesis which is increase by using the curcumin (Alwi *et al.,* 2008). In 18 weeks length of research carried out on LDLR-/- mice to given the consuming routine of high amount of cholesterol and curcumin conc. was used as 0.02% w/w. Curcumin up-regulate the expressions of PPARα then its response to suppress the hepatic triglycerides (TG) accumulation. So, up-regulated genes are very essential in FA oxidation. The consequences of this exhibited that curcumin increases the gene expression of liver X receptor α (LXR α) transcription in liver. Cholesterol-7 α -hydroxylase is regulated through LXR α. That is the important enzyme cholesterol to bile acid conversion. LXR α moreover prompts the ATP-binding cassette. ATP-binding cassette is the sub family of A1 (ABCA1) expression, which enables for cholesterol abolition from peripheral tissues to the liver. Suppressed Hepatic TG accumulation was associated with increased LXR α exercising (Shin *et al.,* 2011). Curcumin verified antihyperlipidemic effects with a number of mechanisms such as, reduce in HMGCo-A reductase enhancement of localization, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and, HMG-CoA reductase inhibition, enlarge liver Apo A-I expression, extend the cholesteryl ester transfer protein (CETP) and Apo B tiers recreation and paraoxonase, acyl coenzyme A, and cholesterol acyltransferase exercise

however these factor out mechanisms are associated with triglycerides decreasing effect (Jang *et al.,* 2008; Shin *et al.,* 2011).

Aloe Vera (Linn.) Burm.f. (Liliaceae)

A mouse model have, the insulin independent diabetes mellitus (DM) the orally administered processed gel of *Aloe vera* using the amounts of 25, 50, and 100mg/kg for eight weeks then it drastically diminished the degree of triglycerides in the liver and also in the plasma level (Kim *et al.,* 2009). The notable study carried out on 5000 patients which were suffering from angina pectoris disease for 5 year. In which *A. vera* had been administered to the patients by this dropped triglycerides level which used to be related to the reduction in the occurrence of anginal attacks (Agarwal *et al.,* 1985).

Anethum Graveolens Linn. (Apiaceae)

A. graveolens vital oil contain limonene (28%), carvone (28%) and α-phellandrene (32%) which have mighty TG lowering efficacy (Hajhashemi & Abbasi, 2008). *A. graveolens* limit the extra serum triglycerides level than cholesterol by a variety of mechanism such as: (i) lowering HMGR fatty acids synthesis and LDL cholesterol suppression (ii) deduction in LDL cholesterol absorption from intestine brush border (iii) uptake of LDL, increasing low density lipid (LDL) receptors, and acetyl-CoA carboxylase inhibition. *A. graveolens* contain the flavonoids that can alter the ratio of low density lipids and high density lipids (Mobasseri *et al.,* 2014).

Apium Graveolens Linn. (Apiaceae)

A. graveolens possess triglycerides lowering property and its hypolipidemic effect facilitated through number of mechanisms including, increasing excretion of fecal bile acid, lipid absorption decline in the intestine, inhibition of hepatic cholesterol biosynthesis, enhancement of plasma lecithin: cholesterol acyltransferase activity. Lipid lowering effect has been shown by the 3-butylphthalideor is a key factor of celery (Mansi *et al.,* 2009).

Commiphora Mukul (Arn.) Bhandari (Burseraceae)

The extract of this plant contains ketonic steroids compounds known as guggulsterones (Ghritlahare *et al.,* 2017). Ketonic steroids compounds such as guggulsterone-Z and guggulsterone-E, accountable for its antilipidemic effect. Guggul-sterones are easily reduced to guggul-sterols in the body which act as robust antioxidants which

have TG reducing property, beside this these compounds show antagonize effect of farnesoid X receptor (FXR), receptor of bile acid, which are crucial regulator of cholesterol homeostasis (Urizar & Moore 2003).

Plantago Ovata Forssk. (Plantaginaceae)

It stimulates the activity of 7 α-hydroxylase enzyme for bile acid synthesis. Fibers of this plant decrease LDL cholesterol by decreasing the LDL cholesterol absorption and also inhibit the hepatic LDL cholesterol synthesis via propionate (Murad *et al.,* 2010) and moreover secondary consequences of slowing glucose absorption (Anderson *et al.,* 2000).

Camellia Sinensis (Linn.) Kuntze (Theaceae)

The active compound of this plant is catechins which possess various pharmacological activities (Esmaeelpanah *et al.,* 2018). Potent factors of tea have potential to inhibition of hepatic lipogenesis, which comprise sterol regulatory element-binding transcription factor 1 (SREBP-1) and its reactive genes without affecting lipoprotein assembly (Shrestha *et al.,* 2009). Catechins decrease the Intestinal absorption of lipids. The catechins, epigallo-catechin gallate (EGCG) are the potentially inhibit the lipids absorption. The inhibitory effects of EGCG is associated interfering with the hydrolysis of fats, luminal emulsification, uptake of lipids and micelle solubilization (Koo & Noh 2007). The catechins inhibit the vital enzymes which is involve in lipids biosynthesis and additionally minimize lipid absorption in intestine as a result enhancing blood lipid profile (Babu *et al.,* 2008).

Glycine Max (Linn.) Merr. (Fabaceae)

G. max contains isoflavones, which have various health benefits. It is particularly reducing LDL cholesterol and triglycerides level in the blood (Taku *et al.,* 2007). Soy protein alternatively diminished the triglycerides and LDL-C in hypercholesterolemic subjects in a manner that is not due to a reduction in LDL cholesterol biosynthesis now. So, it can prove the soy protein have some cholesterolemic metabolism effect. Other mechanisms of soy protein such as suppression of cholesterol, absorption of cholesterol and removing of cholesterol from the tissues excretion of bile acid and improved level of LDL cholesterol (Wang *et al.,* 2004). In a study carried out on 210 type-II diabetic men that obtained soy proteins (30 g) with phytoestrogen (66 mg) then serum triglycerides extensively decline after twelve week of treatment (Sathyapalan & Kilpatrick, 2014).

Andrographis Paniculata (Burm.f.) Nees (Acanthaceae)

The leaves and stem of *A. paniculata* contains andrographolide, a labdane diterpenoids. The andrographolide have amazing hypolipidemic consequences that protect the cardiovascular machine without damaging to the liver with the aid of reducing whole cholesterol, triglycerides, LDL and HDL, in the rats and mice. The refined extracts of *A. paniculata* particularly reduced ranges of glucose in blood, LDL and TG (Jayakumar *et al.,* 2013).

Berberis Aristata DC. and Berberis Vulgaris Linn. (Berberidaceae)

It contains berberine as a compound that is extracted from the plants bark, which reduces cholesterolemia by the way of increasing low density lipid cholesterol receptors on the liver cells surfaces and also inhibit the biosynthesis of triglycerides. *B. vulgaris* is associated in the incensement of (AMPK) adenosine monophosphate-activated protein kinase phosphorylation and also the activity that inhibits the synthesis of cholesterol, fatty acids, triglycerides, β-oxidation and uptake fatty acid (Imenshahidi & Hosseinzadeh, 2016).

Silybum Marianum (Linn.) Gaertn. (Asteraceae)

Silibinin is the main phyto-constituent of this plant. It is shown that its polyphenolic fraction decrease the absorption of cholesterol and triglycerides (Zhang *et al.,* 2013) and also reduces the VLDL synthesis in the liver of the rats (Vaughu *et al.,* 2006).

CONCLUSION

The Problems begin from the insulin resistance and chronic hyperglycemia has emerged as an important subject in the clinical sciences and drugs therapy. Medicinal plants have generally concerned, possibly because of fewer aspect outcomes than the chemically artificial drugs. The anti-hyperglycemic special effects of the vegetation delivered in this chapter are in reality associated to their functionality to maintain the pancreatic function and insulin yield facilitating anabolic matters to do such as adipocyte, muscle, and hepatic glucose uptake as well as glucose to glycogen conversion and additionally in this chapter, we aimed to current a summary of the predominant medicinal vegetation with triglycerides decreasing effect, and the responsible of their family and their lively components. These plants, mainly *N.sativa*, *A. sativum, A. graveolens C. longa*, and *C. mukul* had the exceptional actual Therefore

Table 1. List of the medicinal plants having antidiabetic properties

S.no.	Botanical name	Parts used	References
1	*Persea americana* Mill.	Methanolic leaves extract	Kolawole & Ayankele (2012)
2	*Viscum album* Linn.	Methanolic plant extract	Oluwatosin *et al*., (2008)
3	*Emila praetermissa* Cass.	Aqueous leaves extract	Ngozi *et al.,* (2013)
4	*Solanum anguivi* Lam.	Aqueous fruit extract	Elekofehinti *et al*., (2012)
5	*Nauclea latifolia* Linn.	Ethanolic root, stem and bark extract	Odey *et al*., (2012)
6	*Scoparia dulcis* Linn.	Methanolic whole plant extract	Orhue & Nwanze, (2006)
7	*Vernonia amygdalinum* Delile	Methanolic and ethanolic extract leaves extract	Oluwatosin *et al.,* (2008)
10	*Catharanthus roseus* (Linn.) G.Don	Aqueous leaves extract	Akpan & Okokon, (2005)
11	*Stachytarpheta augustifolia* (Mill.) Vahl	Methanolic aerial part extract	Garba *et al.,* (2013)
12	*Morinda morindoides* Linn.	Methanolic root and bark extract	Olukunle *et al.,* (2012)
14	*Parinari polyandra* Aubl.	Ethanolic fruit extract	Abolaji *et al*., (2007)
15	*Curcuma longa* Linn.	Methanolic rhizomes extract	Nwozo *et al,* (2009)
16	*Croton zambesicus* Burch.	Ethanolic extract from leaf	Ofusori *et al,* (2012)
17	*Bauhinia thonningii* (Sochum.) Milne-Redh.	Aqueous leaves crude extract	Ojezele & Abatan, (2011)
18	*Jatropha tanjorensis* Linn.	Methanolic leaves extract	Oluwole *et al*, (2011)
19	*Garcinia kola* Heckel	Saline root and seed extracts	Udenze *et al.,* (2012)
20	*Carica papaya* Linn.	Aqueous seed extract	Nwangwa & Ekhoye (2013)
21	*Cleistopholis patens* (Benth.) Engl. & Diels	Aqueous leaves extract	Udem *et al*., (2011)
22	*Annona muricata* Linn.	Methanolic plant extract	Adeyemi *et al.,* (2009)
23	*Alchornea cordifolia* Mull. Arg.	Butanolic leaves extract	Mohammed *et al*., (2012)
24	*Moringa oleifera* Lam.	Aqueous leaves extract	Ghasi *et al*., (2000)
25	*Parkia biglobosa* (Jacq.) R.Br. ex G.Don	Methanolic plant extract	Odetola *et al*., (2006)
26	*Cymbopogon citratus* (DC.) Stapf	Aqueous leaves extract	Adeneye & Agbaje, (2007)
28	*Arachis hypogaea* Linn.	Aqueous plant extract	Bilbis *et al.,* (2002)
29	*Xylopia aethiopica* (Dunal) A. Rich.	Methanolic seed extract	Nwozo *et al*., (2011)
31	*Spondias mombin* Linn.	Aqueous leaves extract	Igwe *et al.*, (2008)
32	*Momordica charantia* Linn.	Methanolic fruit extract	Kolawole & Ayankunle (2012)
33	*Cajanus cajan* (Linn.) Millsp.	Methanolic leaves extract	Akinloye & Solanke, (2011)
34	*Melanthera scandens* Rohr	Ethanolic leaves extract	Akpan *et al.*, (2012)

it appears that use of these plants as complementary therapeutics along with nowadays available drugs will enhance the administration of hypertriglyceridemia patients. Finally, it can be concluded that the medicinal plants that produce an associated consequences may additionally moreover be viewed alternative drugs for the therapy or prevention of hyperglycemia and hypertriglyceridemia.

REFERENCES

Abolaji, A. O., Adebayo, A. H., & Odesanmi, O. S. (2007). Effects of *Parinari polyandra* (Rosaceae) on serum lipid profile and some electrolytes in pregnant rabbits. *Research Journal of Medicinal Plant*, *1*(4), 121–127. doi:10.3923/rjmp.2007.121.127

Adeneye, A. A., & Agbaje, E. O. (2007). Hypoglycemic and hypolipidemic effects of fresh leaf aqueous extract of *Cymbopogon citratus* Stapf. in rats. *Journal of Ethnopharmacology*, *112*(3), 440–444. doi:10.1016/j.jep.2007.03.034 PMID:17513076

Adeyemi, D. O., Komolafe, O. A., Adewole, S. O., & Obuotor, E. M. (2009). Anti-hyperlipidemic activities of *Annona muricata* (Linn). *The Internet Journal of Alternative Medicine*, *7*(1), 1–9.

Agarwal, O. P. (1985). Prevention of atheromatous heart disease. *Angiology*, *36*(8), 485–492. doi:10.1177/000331978503600801 PMID:2864002

Akinloye, O. A., & Solanke, O. O. (2011). Evaluation of hypolipidemic and potential antioxidant effects of *Pigeon pea* (*Cajanus cajan* (l) mill sp.) leaves in alloxan-induced hyperglycemic rats. *Journal of Medicinal Plants Research*, *5*, 2521–2524.

Akpan, E. J., Okokon, J. E., & Offong, E. (2012). Antidiabetic and hypolipidemic activities of ethanolic leaf extract and fractions of *Melanthera scandens. Asian Pacific Journal of Tropical Biomedicine*, *2*(7), 523–527. doi:10.1016/S2221-1691(12)60089-6 PMID:23569963

Ali, H., Houghton, P. J., & Soumyanath, A. (2006). α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to *Phyllanthus amarus. Journal of Ethnopharmacology*, *107*(3), 449–455. doi:10.1016/j.jep.2006.04.004 PMID:16678367

Alwi, I., Santoso, T., Suyono, S., Sutrisna, B., Suyatna, F. D., Kresno, S. B., & Ernie, S. (2008). The effect of curcumin on lipid level in patients with acute coronary syndrome. *Acta Medica Indonesiana*, *40*(4), 201–210. PMID:19151449

Amin, B., & Hosseinzadeh, H. (2016). Black cumin (*Nigella sativa*) and its active constituent, thymoquinone: an overview on the analgesic and anti-inflammatory effects. *Planta medica*, *82*(1/2), 816.

Anderson, J. W., Davidson, M. H., Blonde, L., Brown, W. V., Howard, W. J., Ginsberg, H., & Weingand, K. W. (2000). Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *The American Journal of Clinical Nutrition*, *71*(6), 1433–1438. doi:10.1093/ajcn/71.6.1433 PMID:10837282

Andrade-Cetto, A., & Wiedenfeld, H. (2004). Hypoglycemic effect of *Acosmium panamense* bark on streptozotocin diabetic rats. *Journal of Ethnopharmacology*, *90*(2-3), 217–220. doi:10.1016/j.jep.2003.09.049 PMID:15013183

Andreolas, C., da Silva Xavier, G., Diraison, F., Zhao, C., Varadi, A., Lopez-Casillas, F., & Rutter, G. A. (2002). Stimulation of acetyl-CoA carboxylase gene expression by glucose requires insulin release and sterol regulatory element binding protein 1c in pancreatic MIN6 β-cells. *Diabetes*, *51*(8), 2536–2545. doi:10.2337/diabetes.51.8.2536 PMID:12145168

Apostolidis, E., Kwon, Y. I., & Shetty, K. (2007). Inhibitory potential of herb, fruit, and fungal-enriched cheese against key enzymes linked to type 2 diabetes and hypertension. *Innovative Food Science & Emerging Technologies*, *8*(1), 46–54. doi:10.1016/j.ifset.2006.06.001

Arafa, H. M. (2005). Curcumin attenuates diet-induced hypercholesterolemia in rats. *Medical Science Monitor*, *11*(7), BR228–BR234. PMID:15990684

Ashraf, R., Khan, R. A., & Ashraf, I. (2011). Garlic (*Allium sativum*) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. *Pakistan Journal of Pharmaceutical Sciences*, *24*(4), 565–570. PMID:21959822

Babu, A., Pon, V., & Liu, D. (2008). Green tea catechins and cardiovascular health: An update. *Current Medicinal Chemistry*, *15*(18), 1840–1850. doi:10.2174/092986708785132979 PMID:18691042

Bantle, J. P., Wylie-Rosett, J., Albright, A. L., Apovian, C. M., Clark, N. G., Franz, M. J., & Wheeler, M. L. (2008). Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care, 31*, S61-S78.

Bilbis, L. S., Shehu, R. A., & Abubakar, M. G. (2002). Hypoglycemic and hypolipidemic effects of aqueous extract of *Arachis hypogaea* in normal and alloxan-induced diabetic rats. *Phytomedicine*, *9*(6), 553–555. doi:10.1078/09447110260573191 PMID:12403165

Cao, H., Polansky, M. M., & Anderson, R. A. (2007). Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. *Archives of Biochemistry and Biophysics*, *459*(2), 214–222. doi:10.1016/j.abb.2006.12.034 PMID:17316549

Chattopadhyay, R. R. (1993). Hypoglycemic effect of *Ocimum sanctum* leaf extract in normal and streptozotocin diabetic rats. *Indian Journal of Experimental Biology*, *31*(11), 891–893. PMID:8112763

Chuang, C. Y., Hsu, C., Chao, C. Y., Wein, Y. S., Kuo, Y. H., & Huang, C. J. (2006). Fractionation and identification of 9c, 11t, 13t-conjugated linolenic acid as an activator of PPARα in bitter gourd (*Momordica charantia* L.). *Journal of Biomedical Science*, *13*(6), 763–772. doi:10.100711373-006-9109-3 PMID:16955349

Crowther, C. A., Hiller, J. E., Moss, J. R., McPhee, A. J., Jeffries, W. S., & Robinson, J. S. (2005). Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *The New England Journal of Medicine*, *352*(24), 2477–2486. doi:10.1056/NEJMoa042973 PMID:15951574

Crulckshanks, K. J., Orchard, T. J., & Becker, D. J. (1985). The cardiovascular risk profile of adolescents with insulin-dependent diabetes mellitus. *Diabetes Care*, *8*(2), 118–124. doi:10.2337/diacare.8.2.118 PMID:3996168

Di Carli, M. F., Janisse, J., Ager, J., & Grunberger, G. (2003). Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *Journal of the American College of Cardiology*, *41*(8), 1387–1393. doi:10.1016/S0735-1097(03)00166-9 PMID:12706936

Dzib-Guerra, W. D. C., Escalante-Erosa, F., Garcia-Sosa, K., Derbre, S., Blanchard, P., Richomme, P., & Pena-Rodriguez, L. M. (2016). Anti-advanced glycation end-product and free radical scavenging activity of plants from the yucatecan flora. *Pharmacognosy Research*, *8*(4), 276. doi:10.4103/0974-8490.188883 PMID:27695268

Elekofehinti, O. O., Adanlawo, I. G., Salin, J. A., & Sodehinde, S. A. (2012). Saponins from *Solanum anguivi* fruits extracts hypolipidemic potential in Rattusnovergicus. *Der Pharmacia Lettre.*, *4*(3), 811–814.

Esmaeelpanah, E., Razavi, B. M., Vahdati Hasani, F., & Hosseinzadeh, H. (2018). Evaluation of epigallocatechin gallate and epicatechin gallate effects on acrylamide-induced neurotoxicity in rats and cytotoxicity in PC 12 cells. *Drug and Chemical Toxicology*, *41*(4), 441–448. doi:10.1080/01480545.2017.1381108 PMID:29072525

Garba, A., Mada, S. B., Ibrahim, G., Dauran, I. A., & Hamza, A. B. (2013). *Studies on hypoglycemic and hypolipidemic effects of methanolic extract of Stachytarpheta angustifolia (mill) in streptozotoin induced diabetic rats*. *Asian J. Bio. Sci*. doi:10.3923/ajbs.2013

Ghasi, S., Nwobodo, E., & Ofili, J. O. (2000). Hypocholesterolemic effects of crude extract of leaf of *Moringa oleifera* Lam in high-fat diet fed wistar rats. *Journal of Ethnopharmacology*, *69*(1), 21–25. doi:10.1016/S0378-8741(99)00106-3 PMID:10661880

Ghritlahare, S. K., Satapathy, T., Panda, P. K., & Mishra, G. (2017). Ethnopharmacological Story of Guggul Sterones: An Overview. *Research Journal of Pharmacognosy and Phytochemistry*, *9*(3), 182–188. doi:10.5958/0975-4385.2017.00034.6

Ginghina, C., Bejan, I., & Ceck, C. D. (2011). Modern risk stratification in coronary heart disease. *Journal of Medicine and Life*, *4*(4), 377–386. PMID:22514570

Gushiken, L. F., Beserra, F. P., Rozza, A. L., Bérgamo, P. L., Bérgamo, D. A., & Pellizzon, C. H. (2016). Chemical and biological aspects of extracts from medicinal plants with antidiabetic effects. *The Review of Diabetic Studies; RDS*, *13*(2-3), 96–112. doi:10.1900/RDS.2016.13.96 PMID:28012277

Hajhashemi, V., & Abbasi, N. (2008). Hypolipidemic activity of *Anethum graveolens* in rats. Phytotherapy Research. *An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *22*(3), 372–375. PMID:18058989

Igwe, C. U., Ojiako, O. A., Nwaogu, L. A., & Onyeze, G. O. C. (2008). Lipid lowering effect of aqueous leaf extract of *Spondias mombin* Linn. *Journal de Pharmacologie*, *6*(1), 10.

Imenshahidi, M., & Hosseinzadeh, H. (2016). *Berberis vulgaris* and berberine: An update review. *Phytotherapy Research*, *30*(11), 1745–1764. doi:10.1002/ptr.5693 PMID:27528198

Jang, E. M., Choi, M. S., Jung, U. J., Kim, M. J., Kim, H. J., Jeon, S. M., & Lee, M. K. (2008). Beneficial effects of curcumin on hyperlipidemia and insulin resistance in high-fat–fed hamsters. *Metabolism: Clinical and Experimental*, *57*(11), 1576–1583. doi:10.1016/j.metabol.2008.06.014 PMID:18940397

Jayakumar, T., Hsieh, C. Y., Lee, J. J., & Sheu, J. R. (2013). Experimental and clinical pharmacology of *Andrographis paniculata* and its major bioactive phytoconstituent andrographolide. *Evidence-Based Complementary and Alternative Medicine*. PMID:23634174

Joseph, D. (2011). Pharmacotherapy, A pathophysiological approach, 8thedn, *The McGraw Hill companies. Inc.*, *2011*, 370.

Kawa, J. M., Taylor, C. G., & Przybylski, R. (2003). Buckwheat concentrate reduces serum glucose in streptozotocin-diabetic rats. *Journal of Agricultural and Food Chemistry*, *51*(25), 7287–7291. doi:10.1021/jf0302153 PMID:14640572

Kim, K., Kim, H., Kwon, J., Lee, S., Kong, H., Im, S. A., & Park, Y. I. (2009). Hypoglycemic and hypolipidemic effects of processed Aloe vera gel in a mouse model of non-insulin-dependent diabetes mellitus. *Phytomedicine*, *16*(9), 856–863. doi:10.1016/j.phymed.2009.02.014 PMID:19303272

Kolawole, O. T., & Ayankunle, A. A. (2012). Seasonal Variation in the Anti-Diabetic and Hypolipidemic Effects of Momordica charantia Fruit Extract in Rats. *European Journal of Medicinal Plants*, *2*(2), 177–185. doi:10.9734/EJMP/2012/998

Koo, S. I., & Noh, S. K. (2007). Green tea as inhibitor of the intestinal absorption of lipids: Potential mechanism for its lipid-lowering effect. *The Journal of Nutritional Biochemistry*, *18*(3), 179–183. doi:10.1016/j.jnutbio.2006.12.005 PMID:17296491

Kooti, W., Farokhipour, M., Asadzadeh, Z., Ashtary-Larky, D., & Asadi-Samani, M. (2016). The role of medicinal plants in the treatment of diabetes: A systematic review. *Electronic Physician*, *8*(1), 1832–1842. doi:10.19082/1832 PMID:26955456

Kumar, A., Gnananath, K., Gande, S., Goud, E., Rajesh, P., & Nagarjuna, S. (2011). Anti-diabetic Activity of Ethanolic Extract of Achyranthes aspera Leaves in Streptozotocin induced diabetic rats. *Journal of Pharmacy Research*, *4*(7), 3124–3125.

Kumar, D., Parcha, V., Maithani, A., & Dhulia, I. (2012). Effect and evaluation of antihyperlipidemic activity guided isolated fraction from total methanol extract of *Bauhinia variegata* (Linn.) in triton WR-1339 induced hyperlipidemic rats. *Asian Pacific Journal of Tropical Disease*, *2*(2), 909–913. doi:10.1016/S2222-1808(12)60290-4

Kumar, D. B., Mitra, A., & Manjunatha, M. (2011). Azadirachtolide. *Pharmacognosy Communications*, *1*(1), 78–84. doi:10.5530/pc.2011.1.5

Kumar, R., Sharma, B., Tomar, N. R., Roy, P., Gupta, A. K., & Kumar, A. (2011). In vivo evolution of hypoglycemic activity of *Aloe* spp. And identification of its mode of action on GLUT-4 gene expression in vitro. *Applied Biochemistry and Biotechnology*, *164*(8), 1246–1256. doi:10.100712010-011-9210-6 PMID:21409411

Lipinski, B. (2001). Pathophysiology of oxidative stress in diabetes mellitus. *Journal of Diabetes and Its Complications*, *15*(4), 203–210. doi:10.1016/S1056-8727(01)00143-X PMID:11457673

Liu, C., Hu, M. Y., Zhang, M., Li, F., Li, J., Zhang, J., & Liu, X. D. (2014). Association of GLP-1 secretion with anti-hyperlipidemic effect of ginsenosides in high-fat diet fed rats. *Metabolism: Clinical and Experimental*, *63*(10), 1342–1351. doi:10.1016/j.metabol.2014.06.015 PMID:25060691

Liu, L., & Yeh, Y. Y. (2001). Water-soluble organosulfur compounds of garlic inhibit fatty acid and triglyceride syntheses in cultured rat hepatocytes. *Lipids*, *36*(4), 395–400. doi:10.100711745-001-0734-4 PMID:11383692

Mansi, K., Abushoffa, A. M., Disi, A., & Aburjai, T. (2009). Hypolipidemic effects of seed extract of celery (*Apium graveolens*) in rats. *Pharmacognosy Magazine*, *5*(20), 301. doi:10.4103/0973-1296.58149

Manukumar, H. M., Shiva Kumar, J., Chandrasekhar, B., Raghava, S., & Umesha, S. (2017). Evidences for diabetes and insulin mimetic activity of medicinal plants: Present status and future prospects. *Critical Reviews in Food Science and Nutrition*, *57*(12), 2712–2729. doi:10.1080/10408398.2016.1143446 PMID:26857927

Mishra, P. R., Panda, P. K., Apanna, K. C., & Panigrahi, S. (2011). Evaluation of acute hypolipidemic activity of different plant extracts in Triton WR-1339 induced hyperlipidemia in albino rats. *Pharmacologyonline*, *3*, 925–934.

Mobasseri, M., Payahoo, L., Ostadrahimi, A., Bishak, Y. K., Jafarabadi, M. A., & Mahluji, S. (2014). *Anethum graveolens* supplementation improves insulin sensitivity and lipid abnormality in type 2 diabetic patients. *Pharmaceutical Sciences*, *20*(2), 40.

Mohammed, R. K., Ibrahim, S., Atawodi, S. E., Eze, E. D., Suleiman, J. B., & Malgwi, I. S. (2012). The study of the effects of n-butanol fraction of *Alchornea cordifolia* leaf extract on lipid profile and liver enzymes in streptozotocin-induced diabetic rats. *Global Journal of Medicinal Plant Research*, *1*(1), 1–7.

Mollazadeh, H., Cicero, A. F., Blesso, C. N., Pirro, M., Majeed, M., & Sahebkar, A. (2019). Immune modulation by curcumin: The role of interleukin-10. *Critical Reviews in Food Science and Nutrition*, *59*(1), 89–101. doi:10.1080/10408398.2017.1358139 PMID:28799796

Murad, S., Raza, H., & Bashir, A. (2010). Atherosclerosis may be prevented by using psyllium husk. *Pakistan Journal of Medical & Health Sciences*, *4*(3), 255–258.

Nasri, H. (2013). Toxicity and safety of medicinal plants. *Journal of HerbMed Pharmacology, 2*.

Nazarian-Samani, Z., Sewell, R. D., Lorigooini, Z., & Rafieian-Kopaei, M. (2018). Medicinal plants with multiple effects on diabetes mellitus and its complications: A Systematic review. *Current Diabetes Reports*, *18*(10), 72. doi:10.100711892-018-1042-0 PMID:30105479

Ngozi, A. O., Josephine, O. O., & Felicity, E. (2013). Anti-hyperlipidemic effect of aqueous leaf extract of *Emilia praetermissa* milne-redh (Asteraceae) in rats. *International Journal of Biosciences*, *3*(5), 68–77. doi:10.12692/ijb/3.5.68-77

Nwangwa, E. K., & Ekhoye, E. I. (2013). Anti-hyperlipidemic Activity of aqueous extracts of *Carica papaya* seeds in albino rats fed with high fat diet. *Current Trends in Technology and Science*, *II*, 2279.

Nwozo, S. O., Orojobi, B. F., & Adaramoye, O. A. (2011). Hypolipidemic and antioxidant po-tentials of *Xylopia aethiopica* seed extract in hypercholesterolemic rats. *Journal of Medicinal Food*, *14*(1-2), 114–119. doi:10.1089/jmf.2008.0168 PMID:21244241

Odetola, A. A., Akinloye, O., Egunjobi, C., Adekunle, W. A., & Ayoola, A. O. (2006). Possible antidiabetic and antihyperlipidaemic effect of fermented *Parkia biglobosa* (Jacq) extract in alloxan-induced diabetic rats. *Clinical and Experimental Pharmacology & Physiology*, *33*(9), 808–812. doi:10.1111/j.1440-1681.2006.04444.x PMID:16922811

Odey, M. O, Johnson, J. T, Iwara, I. A, Gauje, B, Akpan, N. S, Luke, U. O, Robert, A.E, & Ukpong, K. M. (2012). Effect of anti-hypertensive treatment with root and stem bark extracts on Nauclea latifolia on serum lipid profile. *G.J.P. and A. Sc. and Tech*., *214*, 78-84.

Ofusori, D. A., Komolafe, O. A., Adewole, O. S., Obuofor, E. M., Fakunle, J. B., & Ayoka, A. O. (2012). Effect of ethanolic leaf extract of *Croton zambesicus* (Mull arg.) on lipid profile in streptozotocin-induced diabetic rat. *Diabetologia Croatica*, 41–42.

Ojezele, M. O., & Abatan, O. M. (2011). Hypoglycaemic and coronary risk index lowering effects of Bauhinia thoningii in alloxan induced diabetic rats. *African Health Sciences*, *11*(1), 85–89. PMID:21572862

Olukunle, J. O., Abatan, M. O., Adenubi, O. T., & Amusan, T. A. (2012). Hypoglycaemic and hypolipidaemic effects of crude extracts and chromatographic fractions of *Morinda morindoides* root bark in diabetic rats. *Acta Veterinaria Brno*, *81*(3), 269–274. doi:10.2754/avb201281030269

Oluwatosin, A., Akintayo, O., Achem, J., & Fafun-so, M. A. (2008). Lipid-lowering effects of methanolic extracts of *V. amygdalina* leaves in rats fed on high cholesterol diet. *Journal of the American Medical Association*, *251*, 351–364.

Orhue, N. E. J., & Nwanze, E. A. C. (2006). *Scoparia dulcis* reduces the severity of trypanosome brucei-induced hyperlipidaemia in the rabbit. *African Journal of Biotechnology*, *5*, 883–887.

Oyewole & Akingbala. (2011). Phytochemical analysis and hypolipidemic properties of *Jatropha tanjorensis* leaf extract. *Eur. Journal of Med. Plants*, (4), 180-185.

Perez-Gutierrez, R. M., & Damian-Guzman, M. M. (2012). A potent a-glucosidase and a-amylase inhibitor isolated from *Azadirachta indica* leaves and in vivo antidiabetic property in streptozotocin-nicotinamide-induced type 2 diabetes in mice. *Biological & Pharmaceutical Bulletin*, *35*, 1516–1524. doi:10.1248/bpb.b12-00246 PMID:22975503

Postic, C., Dentin, R., & Girard, J. (2004). Role of the liver in the control of carbohydrate and lipid homeostasis. *Diabetes & Metabolism*, *30*(5), 398–408. doi:10.1016/S1262-3636(07)70133-7 PMID:15671906

Putri, P. E., Mangisah, I., & Suthama, N. (2018). The effect of dietary supplementation of onion and garlic husk powder on protein. *Cholesterol and Fat of Duck Meat.*

Rahier, J., Guiot, Y., Goebbels, R. M., Sempoux, C., & Henquin, J. C. (2008). Pancreatic β-cell mass in European subjects with type 2 diabetes. *Diabetes, Obesity & Metabolism*, *10*, 32–42. doi:10.1111/j.1463-1326.2008.00969.x PMID:18834431

Ramırez-Tortosa, M. C., Mesa, M. D., Aguilera, M. C., Quiles, J. L., Baro, L., Ramirez-Tortosa, C. L., & Gil, A. (1999). Oral administration of a turmeric extract inhibits LDL oxidation and has hypocholesterolemic effects in rabbits with experimental atherosclerosis. *Atherosclerosis*, *147*(2), 371–378. doi:10.1016/S0021-9150(99)00207-5 PMID:10559523

Raskin, P., Ganda, O. P., Schwartz, S., Willard, D., Rosenstock, J., Lodewick, P. A., & McGovern, M. E. (1995). Efficacy and safety of pravastatin in the treatment of patients with type I or type II diabetes mellitus and hypercholesterolemia. *The American Journal of Medicine*, *99*(4), 362–369. doi:10.1016/S0002-9343(99)80182-X PMID:7573090

Sathyapalan, T., Kilpatrick, E. S., Rigby, A. S., Thatcher, N. J., & Atkin, S. L. (2014, June). The effect of soy phytoestrogens on cardiovascular risk markers in men with type 2 diabetes and subclinical hypogonadism-a randomised double blind parallel study. Endocrine Reviews, 35(3).

Shin, S. K., Ha, T. Y., McGregor, R. A., & Choi, M. S. (2011). Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. *Molecular Nutrition & Food Research*, *55*(12), 1829–1840. doi:10.1002/mnfr.201100440 PMID:22058071

Shinde, V., Borkar, A., & Badwaik, R. (2014). Evaluation and comparative study of hypoglycemic activity of aloe Barbadensis Miller with oral hypoglycemic drugs (glibenclamide and metformin) in rats. *International Journal of Medical and Pharmaceutical Sciences*, *4*(6), 31–36.

Shori, A. B. (2015). Screening of antidiabetic and antioxidant activities of medicinal plants. *Journal of Integrative Medicine*, *13*(5), 297–305. doi:10.1016/S2095-4964(15)60193-5 PMID:26343100

Shrestha, S., Ehlers, S. J., Lee, J. Y., Fernandez, M. L., & Koo, S. I. (2009). Dietary green tea extract lowers plasma and hepatic triglycerides and decreases the expression of sterol regulatory element-binding protein-1c mRNA and its responsive genes in fructose-fed, ovariectomized rats. *The Journal of Nutrition*, *139*(4), 640–645. doi:10.3945/jn.108.103341 PMID:19193814

Son, B. K., Kim, J. Y., & Lee, S. S. (2008). Effect of adlay, buckwheat and barley on lipid metabolism and aorta histopathology in rats fed an obesogenic diet. *Annals of Nutrition & Metabolism*, *52*(3), 181–187. doi:10.1159/000138121 PMID:18544971

Sudha, P., Zinjarde, S. S., Bhargava, S. Y., & Kumar, A. R. (2011). Potent α-amylase inhibitory activity of Indian Ayurvedic medicinal plants. *BMC Complementary and Alternative Medicine*, *11*(1), 5. doi:10.1186/1472-6882-11-5 PMID:21251279

Taika, B. B., Bouckandou, M., Souza, A., Bourobou, H. B., MacKenzie, L. S., & Lione, L. (2018). An overview of anti-diabetic plants used in Gabon: Pharmacology and toxicology. *Journal of Ethnopharmacology*, *216*, 203–228. doi:10.1016/j.jep.2017.12.036 PMID:29305175

Taku, K., Umegaki, K., Sato, Y., Taki, Y., Endoh, K., & Watanabe, S. (2007). Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *The American Journal of Clinical Nutrition*, *85*(4), 1148–1156. doi:10.1093/ajcn/85.4.1148 PMID:17413118

Thomson, M., Al-Qattan, K. K., Bordia, T., & Ali, M. (2006). Including garlic in the diet may help lower blood glucose, cholesterol, and triglycerides. *The Journal of Nutrition*, *136*(3), 800–802. doi:10.1093/jn/136.3.800S PMID:16484567

Tomotake, H., Yamamoto, N., Yanaka, N., Ohinata, H., Yamazaki, R., Kayashita, J., & Kato, N. (2006). High protein buckwheat flour suppresses hypercholesterolemia in rats and gallstone formation in mice by hypercholesterolemic diet and body fat in rats because of its low protein digestibility. *Nutrition (Burbank, Los Angeles County, Calif.)*, *22*(2), 166–173. doi:10.1016/j.nut.2005.01.012 PMID:16459229

Tripathi, K. D. (2008). Essentials of Medical Pharmacology, 6thedn, India. *JP Brothers Medical Publishers*, *2008*, 613–614.

Udem, S. C., Ezeonuegbu, U. C., & Obidike, R. I. (2011). Experimental studies on the hypolipidemic and haematological properties of aqueous leaf extract of *Cleistopholiss patens* Benth & Diets. (Annonacae) in hypercholesterolemic rats. *Annals of Medical and Health Sciences Research*, (1): 115–121. PMID:23209964

Udenze, E. C. C., Braide, V. B., Okwesilieze, C. N., & Akuodor, G. C. (2012). Pharmacological effects of *Garcinia kola* seed powder on blood sugar, lipid profile and atherogenic index of alloxan-induced diabetes in rats. *Pharmacologia*, *3*(12), 693–699. doi:10.5567/pharmacologia.2012.693.699

Urizar, N. L., & Moore, D. D. (2003). Gugulipid: A natural cholesterol-lowering agent. *Annual Review of Nutrition*, *23*(1), 303–313. doi:10.1146/annurev.nutr.23.011702.073102 PMID:12626688

Vaughu, C., Gotto, A. J., & Basson, C. T. (2006). The evolving role of silymarin in management of atherosclerosis. *Journal of the American College of Cardiology*, *36*, 1–5.

Wang, Y., Jones, P. J., Ausman, L. M., & Lichtenstein, A. H. (2004). Soy protein reduces triglyceride levels and triglyceride fatty acid fractional synthesis rate in hypercholesterolemic subjects. *Atherosclerosis*, *173*(2), 269–275. doi:10.1016/j.atherosclerosis.2003.12.015 PMID:15064101

Wouters, K., Shiri-Sverdlov, R., van Gorp, P. J., van Bilsen, M., & Hofker, M. H. (2005). Understanding hyperlipidemia and atherosclerosis: Lessons from genetically modified apoe and ldlr mice. *Clinical Chemistry and Laboratory Medicine*, *43*(5), 470–479.

Zhang, W., Hong, R., & Tian, T. (2013). Silymarin's protective effects and possible mechanisms on alcoholic fatty liver for rats. *Biomolecules & Therapeutics*, *21*(4), 264–269. doi:10.4062/biomolther.2013.020 PMID:24244810

Chapter 3
Ethnobotanical and Pharmacological Importance of the Herbal Plants With Anti-Hair Fall and Hair Growth Activities

Kiran Mustafa
The Women University Multan, Pakistan

Javaria Kanwal
The Women University Multan, Pakistan

Sara Musaddiq
Women University Multan, Pakistan

Samia Khakwani
The Women University Multan, Pakistan

ABSTRACT

The primary aim of this study is to access the salient herbal plants with the active constituent of potentially anti-hair fall activities. It also presents the various reasons behind hair loss ailments. As part of this study, a focus is placed on active phytochemicals within these medicinal plants or natural products in terms of various hair fall disease treatments. As natural products have a beneficial effect to minimize hair loss and have promoted the potential for new hair growth, it presents the medicinal values of natural plants in reference to safety and effectiveness for health.

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INTRODUCTION

A term "hair" is used for large series of proteins especially α-keratin flourished from follicles that are encrypted in the corium. Except hairless region, the body of human is blanketed with follicles that are thought to be the cause for developing vellus and terminal hair i.e., short, fine and thick lengthy hair respectively. Hair as a cuticle projection encrypted in the corium and may arise from a tubular appendage that is familiar with the term follicle. The follicle is like a sac residing in cuticle because if a mini finger had squeezed the cuticle into the corium and cardinal hypodermis. Several studies have shown that on human head approximately one to two million hair follicles (Ebling, 1987). In Human lives, hairs have immense importance because of their functionality. There are numerous causes of hair loss in men and women. Several studies have suggested that, it is related to hereditary elements others argue it to be a skin problem (Arakawa, 1962; Adhirajan *et al.,* 2003). The corneal and mental strain may also result in hirsuteness, hair fall and dander (Han & Mirmirani, 2006). Along with other factors, it is found that androgens also contribute to hair loss (Bagatell & Bremner, 1996). Hair loss can also occur because of poor diet, long term disease, variance in thyroid production, chemical actions of contraceptive pills, definite therapies, treatment of cancer via radiations, pregnancy, hereditary inclination and menopause (Olsen & Kadunce, 1997). A large number of drugs such as minoxidil, corticosteroids and dithranol etc. have been used for different types of hair loss. These drugs are linked with different adverse effects like redness of the skin, chronic itchy skin and dental scaling, skin swelling, dryness and itching (Chizick & Delorscio, 1999; Kaushik *et al.,* 2011). Thereby, to tackle the issue of Alopecia, now, we have induced towards the valuable products and searched a lot of herbs that have shown good result. In order to cure Alopecia, mostly herbs are used as they have been found to be useful in terms of sufferer consent, less chance of bad effects and single approach. Many and different approaches such as transfer of organ via operation; chemical and natural products are adopted to cure Alopecia. For hair loss treatment, herbal products are very important as they can provide nutritional support and enhance blood circulation in the scalp.

To promote healthful growth of hair miscellaneous minerals such as Fe, Ca, Cu, Cr, I, Mg and Zn are very important as they enhance the probability of modulation of blood flow however, iron may contribute to toxicity when it is used in excess. Thyroid hormones also play a vital role in reducing the hair fall, dryness and hair pigmentation. Before supplementing the minerals, it is necessary to know which minerals are beneficial for reducing hair loss. Different vitamins such as vitamin-B (particularly folic acid, B6, B3, B5 and), vitamin-E and vitamin-A have remarkable effects on hair growth. Besides this, vitamin-A may also have importance to moisturize the roots of hair it also functions against oxidizing agents and stimulates

the sebaceous gland for its secretion in the head. Vitamin A may contribute to hair falling when used in excess. Vitamin E thought to be indispensable by virtue of its action against oxidizing agent. The property as an antioxidizing agent makes it effective for improving the blood flow in the scalp (Kaushik *et al*., 2011).

Plants and other medicinal herbs are packed with various kinds of minerals, vitamins and other nutrients essential for hair growth and development. It is observed that 5α-Reductase inhibitors, also known as dihydrotestosterone (DHT) blockers are extremely effective against the alopecia. Several herbal products are found to be enriched with DHT-blockers. Different plants like *Urtica dioica* Linn. (Urticulaceae), *Seneroa repens* Hook.f (Arecaceae), and *Panax ginseng* (Baill.) Oken (Araliaceae) are the potent sources of DHT-blockers (Rathnayake & Sinclair, 2010). Alopecia is also treated with concentrated extracts from the various parts of the plants like roots, flowers, leaves and bark. The method of treatment is known as "*aromatherapy*". Different plants such as *Lavandula agustifolia* Mill. (Lamiaceae), *Arnica montana* Linn. (Asteraceae), *Cedrus atlantica* (Endl.) Manetti ex Carriere (Pinaceae), *Oscimum sanctum* Linn. (Lamiaceae), *Rosmarinus officinalis* Spenn. (Lamiaceae), *Pilocarpus jabarondi* Vahl. (Rutaceae) etc. are used for the purpose. Aromatherapy uses essential oils, delivered to the body by smelling or by massaging on the skin. Aromatic oils motivate the follicles for hair growth. These aromatic oils provide the physical and mental relief and also perform functions at the cellular level (Greenish, 1920; Hay *et al.,* 1998).

In the present study different plants which serve as a potential aid against alopecia or promotes hair growth in one way or another are discussed in detail in the light of their ethnobotanical and pharmacological importance.

Aloe barbadensis (Linn) Burm. f. (Asphodelaceae)

Aloe barbadensis is commonly known as Aloe Vera, it releases aloe vera gel from leaves, which is used to make herbal medicine. The extract has depicted remarkable hair growth activity in rats. In a study, *A.barbadensis* showed regeneration of hair-follicles in albino rats suffering from warfarin stimulated hair loss (Semalty *et al.,* 2010). The plant contains numerous bioactive phytochemicals like anthraquinones, flavonoids, phenols, Alkaloids, terpenes and saponins (Kumar *et al.,* 2017). Aloe Vera is named after an Arabic word alloeh which means bitter as the gel present in leaves is bitter in taste. The excellent biological activities of aloe vera have also been documented by several old civilizations like Greek, Egyptian, Persian, African and Indian. Herbal products made from *A. barbadensis* are of core importance in wound healing and in cosmetics. The plant is pharmacologically active in its action against fungus, inflammation, cancer and acts as an immune-regulator. Aloe vera has been collected from East, North and South Africa. Moreover, it is most commonly

grown in torrid and subtropical zone of Caribbean and Latin America. About 500 Aloe species, involving *Aloe perryi* and *Aloe ferox* is present in Socotra Island and Zanzibar respectively (Jamir *et al*., 1999; Semalty *et al*., 2010).

Amaranthus spinosus Linn. (Amaranthaceae)

Herbal plant, *Amaranthus spinosus* packed with zinc, copper, iron and with other mineral supplements, the plant is used against alopecia because of its nutritional value (Kaushik *et al*., 2011). Commonly *A. spinosus* is known as "pig weed" and "spiny amaranth" and also recognized with "Hindi" name "Kate wali Chaulai (kanatabhajii)" usually grown in all over India and Sri Lanka. It is also located in all over the torrid and moderately heated zone of Asia.

A perennial plant, *A. spinosus*, is characterized by vertical and spiny features. Countless varieties are available with flower color ranging from green to purple. According to Ayurveda, it is used as a medicine for the treatment of hair shedding, as a purgative, fever reducing and diuretic agent. Several other researchers claim that *A. spinosus* possess many other biological activities like spasmolytic, hepato-protective, antifertility, antioxidant, antitumor, anti-inflammatory, antimicrobial, bronchodilator, spermatogenic, analgesic and antimalarial properties. It is also used as medicine for value for the treatment of iron-associated anemia, intestinal gas, eating disorders such as anorexia nervosa, and virginal discharge, Hansen's disease, burning pain, hemorrhoids, bronchial inflammation, stomach disorder and biliousness (Kumar *et al.,* 2014).

Hibiscus rosa-sinensis Linn. (Malvaceae)

Hibiscus flowers have been widely researched for the treatment of hair diseases. It is rich in phytochemicals. In a study, several phytochemicals were extracted from the plant with petroleum ether. The extract depicted different biological activities along with excellent hair growth (Adhirajan *et al*., 2003). A group of researches formulated hair herbal oil, with different amounts (2.5%, 5%, 7.5%) of *Hibiscus* powder and coconut oil. The remedy with 7.55% Hibiscus powder plants exhibited best hair growth action as compared to other formulations with a smaller concentration of Hibiscus (Gaur, *et al.,* 2009). Herbal product made from *E. alba*, *H. rosa-sinensis*, and *Nardostachys jatamansi* (D.Don) DC. show rapid hair growth when tested in Wistar albino rats. It was found that the product promotes hair growth by generating new hair follicles (Thorat *et al.,* 2009). *H. rosa-sinensis* is commonly recognized as "gurhal Sanskrit "japa" and Hindi jasum" etc. The plant produces gum from various parts which is enriched with different chemicals such as campesterol, taraxeryl acetate and cholesterol. Gum of hibiscus has been used in beauty products and

for medicinal benefits. Hibiscus roots have been used as a muco-protective agent to relieve cough. Leaves have convincingly shown the moisturizing and soothing effects. Concentrated liquor discharge from Hibiscus roots has been utilized to relieve fever. To accelerate the growth of hair, flowers and leaves of the plant are used. Bark and leaves are used to terminate pregnancy (Kumar, 2013). The plant was originally located in the torrid zone of Asia. China and Japan are also known for the cultivation of *H. rosa-sinensis*. Several important phytochemicals are found in *H. rosa-sinensis* such as anthraquinones, tannins, quinines, flavonoids, phenols, alkaloids, terpenoids, saponins, terpenoids, cardiac glycosides, free amino acids, protein, carbohydrates, reducing sugars, mucilage, aromatic oils and steroids. The pharmacological analyses exhibited that *H. rosa-sinensis* have wide ranging biological activities such as fibrinolytic, reproductive, antidiabetic, anticonvulsant, antioxidant, antiinflammatory, hepatoprotective, antitussive, hypolipidemic, antipyretic, analgesic, immuno-modulatory, antidepressant, memory enhancement, urinary, cytotoxic, dermatological, antiparasitic, anti-hemolytic, neuroprotective, and antimicrobial among many others (Al-Snafi, 2018).

Glycorrhiza glabra Linn. (Fabaceae)

G. glabra is commonly known as licorice. The extract of licorice roots increases the blood flow along with irritation in the scalp. Several studies have been done to evaluate the activity of licorice root extract for hair growth. In a study concentrate of licorice roots was prepared with ether as a solvent. The 2% concentrated extract was applied on female albino rats to promote hair growth. The extract exhibited 76% in hair follicle generation at anagen phase as compared to the 66% growth action of minoxidil and 45% of control group (Upadhyay *et al.,* 2013). Deb *et al.,* (2014) applied licorice extract obtained with 2% solution of water and alcohol on wistar mice to stop hair loss. Licorice extract treated rats shows better results as to the compared to the 2% minoxidil (Saumendu *et al.,* 2014). Licorice has been consumed in Europe since ancient times. *G. glabra* is native in different regions of Asia and southern Europe. Glycyrrhizin is the principal ingredient obtained from licorice roots. It is used abundantly in bakery items and herbal medicine. The plant plays an important role in the treatment of ulcer, diabetes, inflammation, spasmodic disorder and hepatic ailments (Fiore *et al*., 2005). In accordance with the World Health Organization (WHO), *G. glabra* is an important muco-protective agent and is effective against throat infection, coughs and acute bronchitis. It is also proven effective against preventive treatment of indigestion and stomach and intestinal ulcers (Xiaoying *et al.,* 2017).

Citrullus colocynthis (Linn.) Schrad. (Curcubitaceae)

C. colocynthis is known to be effective in pregnancy, diabetes and lipedema. According to Ayurvedic system, it is used as a hair promoting tonic prevents hair fall. Roy *et al.,* (2007) prepared *C. colocynthis* extract by consuming ethanol and petroleum ether. The 2% and 5% concentrated extract was applied to female wistar rats to promote hair growth. The extract exhibited >70% increase in hair follicles at anagen phase as compared to the 67% growth action of minoxidil. To cope with the problem of hair fall, a drug colocynth of commerce is used that is prepared with peeled fruit of *C. colocynthis*. Oil from *C. colocynthis* is used to treat hair pigmentation and hair fall by different ethnic communities. The herbal product formulated by different herbal extracts such as *Cuscuta reflexa*, *E. alba* and *C. colocynthis* has also been used to promote the hair growth (Patel, *et al.,* 2015). The plant is enriched with different phytochemicals such as cucurbitacin E, elatericin B and dihydroelatericin B (Lavie *et al.,* 1964). Albino rats with hair loss due to testosterone were exhibited remarkable hair growth when treated with the indrayan fruit extract (Dhanotia *et al*., 2011). Indrayan belongs to gourd family is broadly distributed in the deserts of the world. Indrayan is effective against different medical disorders such as influenza, cough, diabetes, jaundice, asthma, toothache, joint pain, breast inflammation, wound healing, stomach and intestine ailments (diarrhea, dyspepsia and vomiting), respiratory disorders and microbial diseases. Fruit of *C. colocynthis* is enriched with biologically active phytonutrients like flavonoids, glycosides, alkaloids, fatty acids and aromatic oils. Additionally, bioactive compounds colocynthosides (A and B) and curcurbitacin (A, B, C, D, E, I, J, K, L) are also present in the plant. *C. colocynthis* has wide ranging biological activities such as anti-inflammatory, antilipidemic, insecticide, antimicrobial, antidiabetic, cytotoxic and antioxidant (Hussain *et al*., 2014).

Urtica dioica Linn. (Urticaceae)

U. dioica is commonly known as stinging nettle believed to be effective for promoting hair growth with itching on the scalp. Numerous studies have been conducted on nettle leaves extracts. Several herbal products with nettle leaves extracts have been patented. A US patent App. 13/735,399 reports an herbal product containing copper ions, *S. repens*, *U. dioica*, and *Pygeum* extract, zinc and vitamin B6. The product is reported to remarkably enhance hair growth activity (Schmidt, 2013). Nettle is a biologically active to minimize the action of 5-α-reductase on head skin and inducing hair growth (Lourith & Kanlayavattanakul, 2013). A group of researchers discussed medicinal plants of Iran and explained the species of Urtica to arrest hair fall. Leaves and stems of Stinging nettle is well known to contain bioactive

substance necessary for metabolism and have application in the generation of hair follicles. Rats affecting with wool discharge owing to the administration of boric acids were used as a model to determine hair shedding action and widening of blood vessels. As a consequence of the application of gel consisting of *U. dioica* extract, a remarkable changes occurs in term of increase in wool quantity and discharge of malnourished hair (Pekmezci *et al*., 2018). Various phyto-nutrients such as flavonoids, tannins, volatile compounds, sterols, fatty acids, terpenes, isolectins, polysaccharides, vitamins, proteins, and minerals were found in *U. dioica* (Joshi *et al.,* 2014). Extract of *U. dioica* leaves is enriched with caffeic acid and flavonoids. Concentrate of *U. dioica* leaves acts as antiinflammatory agent and modulate the discharge of pro-inflammatory cytokine followed by retardation nof-protein complex NF-kB pathway (Chrubasik *et al.,*2007). Particularly, leaves of *U. dioica* consist of valuable nutrients i.e. mineral supplements, fatty acids, vitamins essential and amino acids (Rutto *et al.,* 2013).

Emblica officinalis Linn. (Phyllanthaceae)

E. officinalis is traditionally for hair growth activities. *Emblica* is rich in iron, hence providing the oxygen to red blood cells, a prerequisite for healthful hair. It is reported that shortage of iron increases the chances of hair shedding. Extract of *E. officinalis* increase the hair papilla of human scalp which accelerates the hair growth (Luanpitpong *et al.,* 2011).The herbal formulation in the form of oil and lotion with *E. officinalis* as a principal element promotes hair growth and reduces the hair shedding (Banerjee *et al*., 2009; Ishida *et al*., 1999; Purwal *et al.,* 2008). It is found that the mixture of *Tridax procumbens* Linn. (Asteraceae), *Trigonella foenum* Linn. (Fabaceae), *Hibiscus ros*a-sinensis, and *E. officinalis* is extremely effective against hair shedding. *E. officinalis* oil is also considered to be important in terms of its pharmacological abilities. In Ayurveda medicine, *E. officinalis* is thought to be valuable and is recognized as “king of all medicinal plants”. In the Indian traditional medicinal system, it is considered good for heart, liver, bone and blood. *E. officinalis* contains different phytonutrients such as vitamin C, tannins, gallic acid, phyllemblic compounds, carbohydrates, quercetin, polyphenolics, pectin and flavonoids, terpenoids, alkaloids and tannins. *E. officinalis*has wide ranging biological activities such as antigenotoxic, antidepressant, antiulcerogenic, antidepressant, anti-HIV-reverse transcriptase, antimicrobial, anti-inflammatory, antidiabetic, anticarcinogenic and antioxidant (Jain *et al.,* 2016).

Trigonella foenum Linn. (Fabaceae)

T. foenum is commonly known as "Fenugreek". The leaves of the plant are effective against burns, inflammation and hair fall. The plant is enriched with flavonoids, luteolin, quercetin, diosgenin, saponins, tigogenin, trigonelline, gitogenin, 26% proteins, carbohydrates, 6% fat and 44% galactomannan (Prajapati, 2003). Herbal product with *T. foenum* extract (isolated petroleum ether and ethanol) were applied on hairless skin. This result in a significant reduction in time of hair initiation and hair growth. *T. foenum* extract with ethanol also exhibited an increase in the length of hairs (Semalty *et al*., 2010). In an investigation, the mixture of *T. procumbens*, *T. foenum*, *H. rosa*, and *E. officinalis* exhibited accelerated hair growth (Neetu *et al*., 2009). In another study *T. foenum* leave extract isolated from different solvents such as methanol, distilled water, chloroform and pet-ether, showed increase hair growth action in alopecic rats (Imtiaz *et al*., 2017). In medicine, *T. foenum* is found to be effective against different ailments such as diabetes, ulcer, inflammation, fungal and bacterial infection, lipedema, hepatoxicity and cancer (Yadav & Baquer, 2014).

Bacopa monnieri (Linn.) Pennell (Plantaginaceae)

B. monnieri is an herb with the bitter taste and is frequently known as brahmi. The plant is used in traditional Indian medicine for centuries. It contains different phytochemicals such as saponins, alkaloids and sterols. Brahmi is proven to promote hair growth along with the increase in protein kinase action (Shah & Qadri, 1990). A herbal oil formulation made from brahmi showed excellent hair promoting effects (Banerjee *et al*., 2009). The plant is widely cultivated in wetlands and warm regions. Bacopa contains different phytochemicals such as nicotinine, alkaloid brahmine, herpestine, saponins, betulinic acid, saponins A, B and C, bacosides A[3-(α-L-arabinopyranosyl)-O-β-D-glucopyranoside-10,20-dihydroxy-16-keto-dammar-24-ene],stigmastanol, D-mannitol, β-sitosterol, stigmastanol, pseudojujubogenin glycosideand β-sitosterol, *B. monniera* has effective against several medical conditions such as microbial infection, inflammation, heart disorders, nervous conditions (anticonvulsant, antidepressant, memory enhancement, anxiolytic and antiparkinsonian), gastric and intestinal disorders and pain (Chopra *et al.,* 1969; Sastri *et al.,* 1959).

Rosmarinus officinalis Spenn. (Lamiaceae)

R. officinalis is generally known *as* Rosemary. It appeared as a typical thick, perennial and aromatic weed. The plant is extensively used for menstrual cramps and renal disorders. It induces hair follicle growth and provides relief against respiratory

ailments. Essential oil for hair growth promotion is also made from Rosemary along with several other ingredients. Generally, essential oils are delivered to the body by inhalation or by massaging. It is noteworthy that the aromatic oil approaches the blood flow system and works by changing the chemical composition and binding with receptors. It also promotes the growth of hair follicles. The major phytochemical constituents of the plant are borneol, bornyl acetate, camphor, 1,8-cineole, camphorand monoterpenes hydrocarbons (Hay *et al*., 1998). A typical indoor plant, Rosemary is widely distributed in various region of the world. In food, it is used as an aromatizing agent and beverage. In traditional medicine, it acts as a spasmolytic agent, anti-tumor agent, choleretic agent and hepatoprotective agent, and as stimulator for the growth of hair follicles. In addition to this, rosemary extract relaxes different smooth muscles such as trachea and intestine muscles. Extract mainly consist of caffeic and rosmarinic acid both of which have antioxidizing potential. Rosemary extract decreases leukotriene B4 output in polymorphonuclear leucocytes, boost the prostaglandin E2 output. Rosmarinic acid is medicinally valuable, as it is used for the treatment of inflammation, ulcer, cancer, spasmolytic ailments, liver toxicity and heart diseases. It has also proven effective against defective sperm motility and cancer (Al-Sereiti *et al.,* 1999).

Asiasari radix (Aristolochiaceae)

A. radix is commonly known as wild ginger. The major phytochemical constituents of the plant are safrole, methyl eugenol, monoterpenes and methyl eugenol involving a sarinol A, asarinol B, car-3-ene-2, 5-dione,sesamin, asarinin, elemicin and methyleugenol (Rho *et al*., 2005). *A. radix* extract induces hair growth as it has regulatory effects ongene expression and cell growth (Hashimoto *et al*., 1990). In Japan, China and Korea, *A. radix* has been used as a domestic medicine for many centuries. *A. radix*a long with many other herbs is effective against toothache, neuralgia headache, inflammation of gums, bronchospasm, bronchitis and allergies. *A. radix* contains essential oil phenylpropanoids, terpenoids, glycosides and lignins. Pharmacological analysis show that the plant has several biological activities such as antifungal, anti-allergic, antimicrobial and antihepatotoxic, antinflammation, anticytotoxic, antineurotoxic and anticarcinogenic (Ramalingam & Kim, 2015).

Boehmeria nivea (Linn.) Gaudich. (Urticaceae)

B. nivea is an evergreen medicinal plant and has been used as an antipyretic agent. It is also consumed to treat urinary tract disorders. Important phytochemicals in *B. nivea* are chlorogenic acid (10%), fatty acid (10%-30%), protocatechuic acid, linoleic acid, caffeic acid and alphalinolenic acid. Applying *B. nivea* extract, isolated with

acetone solvent on female rat reduces the action of 5-alpha reductase and improves the hair growth activity. Retarding action of 5- alpha reductase was associated with fatty acids which were found to be i.e. palmitic, elaidic, oleic, α-linolenic, linoleic, and stearic acids (Shimizu *et al*., 2000). *B. nivea*, leaves extract has exhibited better inhibition of 5- α-reductase receptor as compared to the standard drug finasteride (Randall & Ebling, 1991).

Ginkgo Biloba Linn. (Ginkgoaceae)

This plant is also called "living fossil" as it is the only remaining species in the genus. *G. biloba* is common herb with health value used in the treatment of wide-ranged disease. It increases the oxygen availability followed by increasing the blood flow to the skin and brain. Bioflavin, lactones, anthrocyanins, sitosteroand ginkgolides A, B, C, J, and M are the principal elements found in *G. biloba*. Extract of Ginkgo and hormones are collectively helpful to improve hair growth.3–35% *Liquiritia officinarum* and 5–40% *Ginkgo biloba* extracts proved to be advantageous in the treatment of hair ailments. Likewise, *Ginkgo* and *Stearyl glycyrrhetinate* extract cooperatively increase the growth of hair and stop hair fall (Patel *et al*., 2015). Leaf extract of *G. biloba* has the ability to accelerate growth of hair again through cell multiplication and programmed-cell death (Kobayashi *et al*., 1993). Leaves extract of *G. biloba* is medicinally important as it functions as an antiviral, antibacterial and antifungal agent because of aldehyde and hydroxylactones present in the leaves (Roychoudhury & Mishra, 2016).

Eclipta alba Linn. (Asteraceae)

Conventionally, it is consumed to reduce hairfall and boost hair growth. Topical application and oral administration of extracted juice of Bhringaraja make the hair black. *E. alba* contains different phytochemicals such as coumestan like demethyl wedelolactone, wedololactone (1.6%), desmethyl-wedelolactone7glucoside and ecliptal-amyrin, luteolin-7-Oglucoside, heptacosanol, hentriacontanol and stigmasterol. Herbal product formulated with *E. alba* is very effective for hair growth (Roy *et al.,* 2007;Sharma *et al*., 2010; Thorat *et al*., 2009). *E. alba* extract isolated by methanol has the potency to accelerate hair growth (Datta *et al*., 2009). Several researchers have shown that extract of *E. alba* with petroleum ether enhance the anagen stage and extend the follicle size (Roy *et al*., 2008). *E. alba*, is normally grown in all over India. The plant is important due to its biological activities and has been consumed for the treatment of epilepsy (Shaikh *et al.,* 2012).

Radix Ginseng C.A. Meyer (Araliaceae)

G. radix is a naturally occurring crude drug. As a conventional drug, it is used to enhance the vitality and provide nutritional support to the body. It is enriched with aromatic oil, ginsenosides, sesquiterpenes, polysaccharides, steroid, choline, vitamin- B, C, E, fatty acid, carbohydrates fatty acid, amino acids, polyacetylenes and peptidoglycans. When tested on rats, red ginseng extract with methanol (70%) depicted better results as compared to the white ginseng extract (Matsuda *et al.,* 2003). In a study, it was found that ginseng inhibits 5-α reductase and promotes hair growth (Liu *et al.,* 2000). By using a model of and rogenetic alopecia, ginsenosides boosted *in vitro* hair growth action because of inhibiting action against 5-α reductase (Murata *et al.,* 2012). Ginseng contains several bioactive substances known as "ginsenosides". The ginsenosides are considered as the active material behind different biological actions of the plant such as anti-inflammation, antioxidation, vasorelaxation and anticancer. About 40 different ginsenoside compounds have been isolated from the plant (Lu *et al.,* 2009).

Sophora flavescens Aiton (Fabaceae)

The extract of *S. flavescens* is well known to contain remarkable hair growth activity. *S. flavescens* extract stimulates the growth factors in the papilla of skin cells which in return promotes the hair growth. Moreover, the extract also showed the 5-alpha reductase type II inhibition (Roh *et al*., 2002). *S. flavescens* is known as "kushen" and in Chinese medicine; it has been considered valuable species since 220AD. In conventional medicine of various countries like Japan, China, India, Korea and European countries, *S. flavescens* in herbal formulations.

In traditional Chinese medicine it is used to treat diarrhea, inflammation, eczema, hematochezia, jaundice, oliguria, female genital inflammation, asthma, atopic dermatitis, ulcers and dermal disorders. About 200 different phytochemicals have been isolated from *S. flavescens*. Phytochemicals obtained from *S. flavescens* possess different biological activities such as antitumor, antipyretic, antinociceptive and anti-inflammatory and antimicrobial (He *et al.,* 2015).

CONCLUSION

Hair loss or baldness is genuine and regularly developing inconvenience in terms of beauty and health. In order to solve the problem, synthetic drugs like minoxidil and finasteride are available in the market however, they come with several side effects like itching and redness of the skin. So, in order to cope with the problem scientist

have been looking towards the natural sources. There are several plants and herbs which are effective against hair loss. The current chapter has elaborated several such plants in light of the mode of action for controlling hair loss and promoting hair growth along with their ethnobotanical and pharmacological importance.

REFERENCES

Adhirajan, N., Kumar, T. R., Shanmugasundaram, N., & Babu, M. (2003). *In vivo* and *in vitro* evaluation of hair growth potential of *Hibiscus rosa-sinensis* Linn. *Journal of Ethnopharmacology*, *88*(2-3), 235–239. doi:10.1016/S0378-8741(03)00231-9 PMID:12963149

Al-Sereiti, M. R., Abu-Amer, K. M., & Sena, P. (1999). *Pharmacology of rosemary (*Rosmarinus officinalis *Linn.) and its therapeutic potentials*. Academic Press.

Al-Snafi, A. E. (2018). Chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa-sinensis* -A review. *Journal of Pharmaceutics*, *8*(7), 101–119.

Arakawa, T. (1962). Effect of Swertinogen on hair growth with special reference to its activities on skin function. *The Tokushima Journal of Experimental Medicine*, *9*, 37–59. PMID:14013531

Bagatell, C. J., & Bremner, W. J. (1996). Androgens in men-uses and abuses. *The New England Journal of Medicine*, *334*(11), 707–715. doi:10.1056/NEJM199603143341107 PMID:8594431

Banerjee, P. S., Sharma, M., & Nema, R. K. (2009). Preparation, evaluation and hair growth stimulating activity of herbal hair oil. *Journal of Chemical and Pharmaceutical Research*, *1*, 261–267.

Chizick, S., & Delorscio, R. (1999). *Natural preparation for treatment of male pattern hair loss*. Google Patents.

Chopra, R. N., Chopra, I. C., & Varma, B. S. (1969). *Glossary of Indian Medicinal Plants/Supplement*. Council of Scientific & Industrial Research.

Chrubasik, J. E., Roufogalis, B. D., Wagner, H., & Chrubasik, S. (2007). A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: Urticae radix. *Phytomedicine*, *14*(7-8), 568–579. doi:10.1016/j.phymed.2007.03.014 PMID:17509841

Datta, K., Singh, A. T., Mukherjee, A., Bhat, B., Ramesh, B., & Burman, A. C. (2009). *Eclipta alba* extract with potential for hair growth promoting activity. *Journal of Ethnopharmacology*, *124*(3), 450–456. doi:10.1016/j.jep.2009.05.023 PMID:19481595

Dhanotia, R., Chauhan, N. S., Saraf, D. K., & Dixit, V. K. (2011). Effect of *Citrullus colocynthis* Schrad fruits on testosterone-induced alopecia. *Natural Product Research*, *25*(15), 1432–1443. doi:10.1080/14786410802632820 PMID:19764005

Ebling, F. J. (1987). The biology of hair. *Dermatologic Clinics*, *5*(3), 467–481. doi:10.1016/S0733-8635(18)30728-9 PMID:3301105

Fiore, C., Eisenhut, M., Ragazzi, E., Zanchin, G., & Armanini, D. (2005). A history of the therapeutic use of liquorice in Europe. *Journal of Ethnopharmacology*, *99*(3), 317–324. doi:10.1016/j.jep.2005.04.015 PMID:15978760

Gaur, K., Kori, M. L., & Nema, R. K. (2009). Comparative screening of immunomodulatory activity of hydro-alcoholic extract of *Hibiscus rosa sinensis* Linn. and ethanolic extract of Cleome gynandra Linn. *Global Journal of Pharmacology*, *3*(2), 85–89.

Greenish, H. G. (1920). *A Text Book of Materia Medica: Being an Account of the More Important Crude Drugs of Vegetable and Animal Origin*. J. & A. Churchill.

Han, A., & Mirmirani, P. (2006). *Clinical approach to the patient with alopecia*. Academic Press.

Hashimoto, K., Katsuhara, T., Itoh, H., Ikeya, Y., Okada, M., & Mitsuhashi, H. (1990). Monoterpenes from asiasari radix from *Asiasarum* sp. *Phytochemistry*, *29*(11), 3571–3574. doi:10.1016/0031-9422(90)85278-N

Hay, I. C., Jamieson, M., & Ormerod, A. D. (1998). Randomized trial of aromatherapy: Successful treatment for alopecia areata. *Archives of Dermatology*, *134*(11), 1349–1352. doi:10.1001/archderm.134.11.1349 PMID:9828867

He, X., Fang, J., Huang, L., Wang, J., & Huang, X. (2015). *Sophora flavescens* Ait.: Traditional usage, phytochemistry and pharmacology of an important traditional Chinese medicine. *Journal of Ethnopharmacology*, *172*, 10–29. doi:10.1016/j.jep.2015.06.010 PMID:26087234

Hussain, A. I., Rathore, H. A., Sattar, M. Z. A., Chatha, S. A. S., Sarker, S. D., & Gilani, A. H. (2014). *Citrullus colocynthis* (L.) Schrad (bitter apple fruit): A review of its phytochemistry, pharmacology, traditional uses and nutritional potential. *Journal of Ethnopharmacology*, *155*(1), 54–66. doi:10.1016/j.jep.2014.06.011 PMID:24936768

Imtiaz, F., Islam, M., Saeed, H., Saleem, B., Asghar, M., & Saleem, Z. (2017). Impact of *Trigonella foenum-graecum* Leaves Extract on Mice Hair Growth. *Pakistan Journal of Zoology*, *49*(4), 1405–1412. doi:10.17582/journal.pjz/2017.49.4.1405.1412

Ishida, H., Inaoka, Y., Okada, M., Fukushima, M., Fukazawa, H., & Tsuji, K. (1999). Studies of the Active Substances in Herbs Used for Hair Treatment. III. Isolation of Hair-Regrowth Substances from *Polygara senega* var. *latifolia* Torr. (Gray). *Biological & Pharmaceutical Bulletin*, *22*(11), 1249–1250. doi:10.1248/bpb.22.1249 PMID:10598039

Jahan, R., Al-Nahain, A., Majumder, S., & Rahmatullah, M. (2014). Ethnopharmacological significance of *Eclipta alba* (L.) hassk. (Asteraceae). *International Scholarly Research Notices*, 2014. PMID:27355071

Jain, P. K., Das, D., Pandey, N., & Jain, P. (2016). Traditional Indian herb *Emblica officinalis* and its medicinal importance. *Innov J Ayurvedic Sci*, *4*(4), 1–15.

Jamir, T. T., Sharma, H. K., & Dolui, A. K. (1999). Folklore medicinal plants of Nagaland, India. *Fitoterapia*, *70*(4), 395–401. doi:10.1016/S0367-326X(99)00063-5

Joshi, B. C., Mukhija, M., & Kalia, A. N. (2014). Pharmacognostical review of *Urtica dioica* L. *International Journal of Green Pharmacy*, *8*(4).

Kaushik, R., Gupta, D., & Yadav, R. (2011). Alopecia: Herbal remedies. *International Journal of Pharmaceutical Sciences and Research*, *2*(7), 1631.

Kobayashi, N., Suzuki, R., Koide, C., Suzuki, T., Matsuda, H., & Kubo, M. (1993). Effect of leaves of *Ginkgo biloba* on hair regrowth in C3H strain mice. *Yakugaku zasshi*. *Journal of the Pharmaceutical Society of Japan*, *113*(10), 718–724. doi:10.1248/yakushi1947.113.10_718 PMID:8254481

Kumar, D. (2013). *Pharmaceutical and pharmacological activities of Hibiscus rosa sinensis mucilage* (vol. 2). Academic Press.

Kumar, R. P., Shammy, J., Nitin, G., & Rinu, R. (2014). An inside review of *Amaranthus spinosus* Linn: A potential medicinal plant of India. *International Journal of Research in Pharmacy and Chemistry*, *4*(3), 643–653.

Kumar, S., Yadav, A., Yadav, M., & Yadav, J. P. (2017). Effect of climate change on phytochemical diversity, total phenolic content and *in vitro* antioxidant activity of *Aloe vera* (L.) Burm.f. *BMC Research Notes*, *10*(1), 60. doi:10.118613104-017-2385-3 PMID:28118858

Kwon, O. S., Han, J. H., Yoo, H. G., Chung, J. H., Cho, K. H., Eun, H. C., & Kim, K. H. (2007). Human hair growth enhancement *in vitro* by green tea epigallocatechin-3-gallate (EGCG). *Phytomedicine*, *14*(7-8), 551–555. doi:10.1016/j.phymed.2006.09.009 PMID:17092697

Lavie, D., Willner, D., & Merenlender, Z. (1964). Constituents of *Citrullus colocynthis* (L.) Schrad. *Phytochemistry*, *3*(1), 51–56. doi:10.1016/S0031-9422(00)83994-1

Liu, W. K., Xu, S. X., & Che, C.-T. (2000). Anti-proliferative effect of ginseng saponins on human prostate cancer cell line. *Life Sciences*, *67*(11), 1297–1306. doi:10.1016/S0024-3205(00)00720-7 PMID:10972198

Lourith, N., & Kanlayavattanakul, M. (2013). Hair loss and herbs for treatment. *Journal of Cosmetic Dermatology*, *12*(3), 210–222. doi:10.1111/jocd.12051 PMID:23992163

Lu, J.-M., Yao, Q., & Chen, C. (2009). Ginseng compounds: An update on their molecular mechanisms and medical applications. *Current Vascular Pharmacology*, *7*(3), 293–302. doi:10.2174/157016109788340767 PMID:19601854

Luanpitpong, S., Nimmannit, U., Pongrakhananon, V., & Chanvorachote, P. (2011). *Emblica* (*Phyllanthus emblica* Linn.) fruit extract promotes proliferation in dermal papilla cells of human hair follicle. *Research Journal of Medicinal Plant*, *5*(1), 95–100. doi:10.3923/rjmp.2011.95.100

Matsuda, H., Yamazaki, M., Asanuma, Y., & Kubo, M. (2003). Promotion of hair growth by ginseng radix on cultured mouse vibrissal hair follicles. *Phytotherapy Research*, *17*(7), 797–800. doi:10.1002/ptr.1241 PMID:12916080

Murata, K., Takeshita, F., Samukawa, K., Tani, T., & Matsuda, H. (2012). Effects of ginseng rhizome and ginsenoside Ro on testosterone 5α-reductase and hair re-growth in testosterone-treated mice. *Phytotherapy Research*, *26*(1), 48–53. doi:10.1002/ptr.3511 PMID:21538628

Neetu, S., Dhanila, V., Rakesh, B., Anjali, K., Ashish, J., & Sanjay, J. (2009). Development and evaluation of polyherbal formulations for hair growth activity. *Pharmacognosy Journal*, *1*(2), 165–170.

Olsen, E. A., & Kadunce, D. P. (1997). Disorders of hair growth: Diagnosis and treatment. *Journal of the American Academy of Dermatology*, *36*(5), 804–804.

Patel, S., Sharma, V. S., Chauhan, N., Thakur, M., & Dixit, V. K. (2015). Hair growth: Focus on herbal therapeutic agent. *Current Drug Discovery Technologies*, *12*(1), 21–42. doi:10.2174/1570163812666150610115055 PMID:26058803

Pekmezci, E., Dundar, C., & Turkoglu, M. (2018). Proprietary herbal extract downregulates the gene expression of IL-1α in HaCaT cells: Possible implications against nonscarring alopecia. *Medicinski Arhiv*, *72*(2), 136. doi:10.5455/medarh.2018.72.136-140 PMID:30302033

Prajapati, N. D. (2003). *Handbook of Medicinal Plants: A Complete Source*. Agrobios.

Purwal, L., Gupta, S. P. B. N., & Pande, S. M. (2008). Development and evaluation of herbal formulations for hair growth. *Journal of Chemistry*, *5*(1), 34–38.

Ramalingam, M., & Kim, S.-J. (2015). Phytochemical, toxicological and pharmacological studies of *Asiasari Radix*: A Review. *Tropical Journal of Pharmaceutical Research*, *14*(3), 545–554. doi:10.4314/tjpr.v14i3.26

Randall, V. A., & Ebling, F. J. G. (1991). Seasonal changes in human hair growth. *British Journal of Dermatology*, *124*(2), 146–151. doi:10.1111/j.1365-2133.1991.tb00423.x PMID:2003996

Rathnayake, D., & Sinclair, R. (2010). Male androgenetic alopecia. *Expert Opinion on Pharmacotherapy*, *11*(8), 1295–1304. doi:10.1517/14656561003752730 PMID:20426708

Rho, S.-S., Park, S.-J., Hwang, S.-L., Lee, M.-H., Kim, C. D., Lee, I.-H., ... Rang, M. (2005). The hair growth promoting effect of Asiasari radix extract and its molecular regulation. *Journal of Dermatological Science*, *38*(2), 89–97. doi:10.1016/j.jdermsci.2004.12.025 PMID:15862941

Roh, S.-S., Kim, C. D., Lee, M.-H., Hwang, S.-L., Rang, M.-J., & Yoon, Y.-K. (2002). The hair growth promoting effect of Sophora flavescens extract and its molecular regulation. *Journal of Dermatological Science*, *30*(1), 43–49. doi:10.1016/S0923-1811(02)00060-9 PMID:12354419

Roy, R. K., Thakur, M., & Dixit, V. K. (2007). Development and evaluation of polyherbal formulation for hair growth–promoting activity. *Journal of Cosmetic Dermatology*, *6*(2), 108–112. doi:10.1111/j.1473-2165.2007.00305.x PMID:17524127

Roy, R. K., Thakur, M., & Dixit, V. K. (2007). Effect of citrullus colocynthis. On hair growth in albino rats. *Pharmaceutical Biology*, *45*(10), 739–744. doi:10.1080/13880200701585709

Roy, R. K., Thakur, M., & Dixit, V. K. (2008). Hair growth promoting activity of *Eclipta alba* in male albino rats. *Archives of Dermatological Research*, *300*(7), 357–364. doi:10.100700403-008-0860-3 PMID:18478241

Roychoudhury, N., & Mishra, R. (2016). *Ginko biloba* Linn.: A promising species of potential importance. *Van Sangyan*, *3*, 35–37.

Rutto, L. K., Xu, Y., Ramirez, E., & Brandt, M. (2013). Mineral properties and dietary value of raw and processed stinging nettle (*Urtica dioica* L.). *International Journal of Food Sciences*. PMID:26904610

Schmidt, A. (2013). *Composition and uses for influencing hair growth*. Google Patents.

Semalty, M., Semalty, A., Joshi, G. P., & Rawat, M. S. M. (2010). *In vivo* hair growth activity of herbal formulations. *International Journal of Pharmacology*, *6*, 53–57. doi:10.3923/ijp.2010.53.57

Shah, C. S., & Qadri, J. S. (1990). *Text book of pharmacognosy (Shah, BS), prakashan*. Academic Press.

Shaikh, M. F., Sancheti, J., & Sathaye, S. (2012). Phytochemical and pharmacological investigations of *Eclipta alba* (Linn.) Hassak leaves for antiepileptic activity. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(4), 319–323.

Sharma, A. K., Agarwal, V., Kumar, R., Kaushik, K., Bhardwaj, P. H., & Chaurasia, H. (2010). Development and evaluation of herbal formulation for hair growth. *International Journal of Current Trends in Science and Technology*, *1*, 147–151.

Thorat, R. M., Jadhav, V. M., & Kadam, V. J. (2009). Development and evaluation of polyherbal formulations for hair growth-promoting activity. *International Journal of Pharm Tech Research*, *1*(4), 1251–1254.

Upadhyay, S., Upadhyay, P., Vinode, R., & Dixit, V. K. (2013). Effect of ethanolic fraction of Hibiscus rosa sinensis l., leaves in androgenic alopecia. *Egyptian Dermatology Online Journal*, *9*(5), 2.

Xiaoying, W., Han, Z., & Yu, W. (2017). Glycyrrhiza glabra (Licorice): ethnobotany and health benefits. In Sustained Energy for Enhanced Human Functions and Activity (pp. 231-250). Academic Press.

Yadav, P., Verma, P., Khandelwal, N., & Prajapati, P. K. (2012). Clinical evaluation of kesharaja taila in the management of khalitya. *Endocrine*, *5*, 10.

Yadav, U. C. S., & Baquer, N. Z. (2014). Pharmacological effects of *Trigonella foenum-graecum* L. in health and disease. *Pharmaceutical Biology*, *52*(2), 243–254. doi:10.3109/13880209.2013.826247 PMID:24102093

Chapter 4
Medicinal Plants:
A Potent Source of Diuretics and Antioxidants in Traditional Medicinal Systems

Aashaq Hussain Bhat
Chaudhary Charan Singh University, Meerut, India

Himani Sharma
Chaudhary Charan Singh University, Meerut, India

ABSTRACT

Medicines of plant origin have been used for treating humans and animals without any adverse effects. New medicinal plants are searched to develop more effective and cheaper drugs in place of synthetics drugs. Plants represent a large natural source of compounds that might serve for the development of novel drugs. Currently medicinal herbs are researched for diuretic properties, and several medicinal herbs are used as diuretics. Currently various synthetic medicines are available for this purpose; however, natural resource medicines are still an important choice because of their higher efficiency and better safety. Further, some herbs are also important sources of antioxidants, which protect the body from the effects of free radicals produced in the body. Antioxidants are required by our body due to increase in the likely exposure of the body to harmful pollutants, radiation, UV lights, etc. These have the ability to delay the oxidation, and plant-derived products are of great interest due to the adverse effect of antibiotics.

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INTRODUCTION

Currently, the usage and attention of people towards the treatment of diseases through natural plant remedies has diverted the attention of researchers and pharmacologists in investigating medicinal values of herbs and other plants. The foundation of traditional medicinal systems of India *viz*., Siddha, Ayurveda, Unani and folk are primarily based on plants or their products. Natural drugs obtained from herbs are safe and cost-effective, and their applications in many therapies have established these facts. These plants synthesize various chemical compounds, which have medicinal properties and thus are used in drug development.

The practice of treating diseases by medicines of herbal origin has been increased enormously and two-thirds of the world's population use herbal medicinal products for primary healthcare. Many countries around the world have produced a variety of effective drugs to treat infections and their use all over world is increasing. Some medicinal plants are currently investigated for diuretic and antioxidant actions, and many have been known to have potent diuretic and antioxidant properties. Treatment of the diseases by employing synthetic drugs on one hand give relief to body, but simultaneously they lead to various side effects, and more chances of reemergence of the disease. Various medicinal plants have been observed to show diuretic and antioxidant assets and researches are continuing to find other plants having these potentials. This chapter highlights the diuretic and antioxidant properties of some medicinal herbs and their role in treating different ailments in the human body.

DIURETICS AND THEIR TYPES

Diuretics are drugs or any substances which have characteristic feature of increasing the output of urine in animals by slowing down the renal reabsorption of water. Diuretics possess a remarkable property of increasing the diuresis by inhibiting the Na^+ reabsorption in the proximal and distal convoluted tubule of nephrons. Three basic processes are responsible for the increased urine excretion and electrolytes by the kidneys *viz*., glomerular filtration, tubular reabsorption (active and passive) and tubular secretion and thus regulate the water and electrolyte balance in the body. Diuretics are liable for the increased excretion of fluids in the urine.

Diuretics are very effective in the treatment of cardiac oedema, specifically the one related with congestive heart failure. They are employed extensively in various types of disorders, for example, nephritic syndrome, diabetes insipidus, nutritional oedema, cirrhosis of the liver, influenza, water poisoning, hypertension, oedema of pregnancy and also to lower intraocular and cerebrospinal fluid pressure and certain kidney diseases (Barrar, 2003).

Diuretics show a significant role in the management of oedema and hypertension by increasing net negative water and solute balance. About 50-66% of fluid is reabsorbed by the proximal convoluted tubule of nephron via both active and passive processes. It has been observed that the thin descending limb of Henle's loop permits osmotic water abstraction as it is highly permeable to water and impermeable to solutes. Further from descending limb of loop of Henle, there is less water absorption which plays an important role in overall enhanced condition of diuresis. Finally, the thin ascending limb of loop of Henle is impermeable to water and highly permeable to chloride and sodium, therefore, diuretics show no effects on it (Kokko, 1984).

Types of Diuretics

Basically there are three types of diuretics currently in use: thiazide, loop and potassium-sparing. All the three diuretics are responsible for the increased excretion of solutes in urine. These diuretics specifically targets different parts of nephron, and thus, have different uses with different side effects and thus preliminary precautions must be taken before using them.

Thiazide Diuretics

Most commonly used and approved diuretics used today are thiazides, being mostly used in curing of high blood pressure. One of the thiazides *viz*., chlorthiazide promotes the loss of sodium and chloride ions by specifically targeting the distal convoluted tubule of the nephron through the inhibition of sodium-chloride symporters. These drugs with other medications are exploited for lowering the blood pressure. The other commonly used thiazides include: metolazone, hydrochlorothiazide (Microzide), indapamide, chlorthalidone, etc. All of these thiazides help in lowering blood pressure by relaxing and relieving fluids

Loop Diuretics

The condition of heart failure is often treated by employing loop diuretics. One of the loop diuretics often prescribed is furosemide which selectively inhibits the sodium-potassium-chloride symporters located in the ascending limb of loop of Henle to elevate the urine flow. Torsemide (Demadex), bumetanide are other frequently used loop diuretics.

Potassium-Sparing Diuretics

Potassium-sparing diuretics, as the name suggests are a type of diuretics which have the ability to eradicate the fluid in the urine without losing the potassium ions. These diuretics can be differentiated from other diuretics in terms of the potassium loss. Potassium is one of the key nutrients required by the body and loss of this nutrient lead to many heath concerns e.g., arrhythmia. Potassium sparing diuretics are recommended for those patients who are at risk of low potassium levels or are taking other medicines which lower potassium levels in their body. Therefore, physicians usually prescribed potassium sparing diuretics along with other medications as these diuretics don't lower the blood pressure. The commonly used potassium-sparing diuretics are spironolactone (Aldactone), triamterene (Dyrenium), eplerenone (Inspra), amiloride etc.

MEDICINAL HERBS WITH DIURETIC PROPERTIES

The preparations of medicinal plants which are used as diuretics comprises of mono-herbal or poly-herbal preparations. It is estimated that more than 650 mono- and poly-herbal preparations from more than 75 plants which are in clinical use today are available in the form of decoction, tincture, tablets and capsules. Some well documented examples of plants having diuretic properties are as follows.

Mangifera indica Linn. (Anacardiaceae)

It is indigenous to Indian landscape and mostly grown in the warm geographical areas. The fruit of this tree, mango is the national fruit of India as well as it is one of the tallest trees in the world. This plant contains constituents which have diuretic activities. The diuretic property of plant bark extract was studied by Shree Devi (2011) in rats. In this experiment, she used the metabolites obtained from the bark of this plant prepared either in water or ethanol or ethyl acetate to study its diuretic properties. The diuretic properties of these plants extracts were studied by measuring the urine volume in rats at different interval of times such as 1h, 2h, 4h, 6h, 24h etc. For positive control purposes, furosemide (20mg/kg) i.p. and mannitol (100mg/kg) i.v. were used. The extract derived from the mango plant (at the dose of 250 mg/kg body weight) was given orally. From this study, Shree Devi found that the ratio of Na+/ K+ was highest in the aqueous extract and lower in ethanol and ethyl acetate extracts. Among all the extracts, aqueous extracts found to possess good diuretic properties in comparison to other two.

Mimosa pudica Linn. (Fabaceae)

It is commonly known as touch-me-not plant or shy plant as its leaves have characteristic feature of inward folding when touched or shaken by the arms or hands and re-open in few minutes. It is very sensitive plant and this feature of inward folding and droop when touched is used by the plant in order to protect itself from predators. It is a creeping flowering herb and indigenous to South America and Central America. These herbs grow well under shrubs or trees as well as in shady areas and thus belong to sciophytes. The extract of this plant has been found to show diuretic activities. In a study, albino rats were fed normally on the aqueous extract derived from the *M. pudica* leaves using the Lipschitz test (Lipschitz *et al.,* 1943) while control group were fed on 0.9% NaCl. The tested groups of albino rats were divided into three groups and these groups were treated with different doses of the aqueous extract *i.e.*, 100, 200 and 400 mg/kg respectively. The standard group was maintained by providing furosemide (Sangmai *et al.,* 2010). The study revealed that the groups treated with 100 mg/kg p.o. showed substantial diuretic activity with improved electrolyte excretion. This study thus pointed out that the diuretic properties of this extract or drug doesn't increase with the increase in dose.

Lepidium sativum Linn. (Brassicaceae)

It is also known as garden cress, halim or common cress. It is an annual upright plant and profusely-branched that reaches up to a height of 80cm. Volatile oils are found in the seeds and leaves of this plant. Seeds of the garden cress are bitter and possess a variety of characteristic attributes such as antihistaminic, diuretic, antibacterial activities as well as they act as gastrointestinal stimulants, gastroprotective, stomachic, laxative, aphrodisiac, antiscorbutic, galactogogue, thermogenic, rubefacient, depurative, tonic, ophthalmic, expectorant (Baquar, 1989; Duke *et al.*, 2002). The seeds of this plant are assumed to be a good medicinal remedy in various countries for treating respiratory disorders, like asthma, bronchitis and cough (Kloos, 1976). Recent studies suggests that they are not only useful in the treatment of respiratory disorders but also efficacious against poultices for sprains, coughs with expectoration, leucorrhoea, leprosy, splenomegaly, lumbago, diarrhea, seminal weakness and scurvy. Glycosides, alkaloids sterols, glucosinolate, flavonoids, triterpenes, glucotropaeolin and coumarins are the major chemical compounds present in the *L. sativum* (Archana & Anita 2006).

The diuretic properties of this plant were observed by Patel (2009). Aqueous and methanolic extracts prepared from the *L. sativum* were found to show diuretic activities as they elevated excretion of the sodium, however, the aqueous extract also played an important role in the excretion of potassium with the methanol extract

showing potassium conserving nature. Diuretic properties of methanolic and aqueous extract of this plant were comparable to that of the hydrochlorothiazide, used as a reference drug.

Achyranthes aspera Linn. (Amaranthaceae)

Achyranthes aspera, prickly chaff flower, chaff-flower or devil's horsewhip are the commonly used names for the *A. aspera*. This plant usually grows on the waysides on roads as a weed plant (Zafar, 2009). Traditionally, this plant was used for curing number of human ailments and is well-known plant in the various medicinal systems such as Allopathic, Siddha, Ayurveda, Unani-Tibbi, Homeopathic, Home Remedies and Naturopathic (Dhale *et al.,* 2013). The plant is exploited for its various properties such as anti-allergic, cardiovascular, spermicidal, nephroprotective, antiparasitic, hypoglycemic, diuretic, cancer chemo-preventive, hepatoprotective, analgesic and antipyretic (Paul *et al.,* 2010; Datir *et al.,*2009).

Srivastav *et al.,* (2011) evaluated the diuretic potential of this whole plant, *A. aspera* using methanolic extract. The diuretic effect of the drugs was screened by the Lipschitz method (Lipschitz *et al.*, 1943) in which furosemide was used as a standard drug. The rats which were treated with the methanolic extracts of the plant showed high diuretic effects as compared to the control, however, this effect were less than the standard furosemide. It has been observed that there was an increase in the elimination of the sodium, potassium and chloride ions in treated and standard population of the rats.

Bixa orellana Linn. (Bixaceae)

It is an indigenous plant of Brazil but also cultivated in other geographical areas such as South and Central America, East Africa, Ecuador, Indonesia, Mexico, India, Kenya and Peru (Elias *et al.,* 2002). One of the important features of this plant observed by pharmacologists was that they are a source of dyes (derived from the seeds of this plant) which are used in textile, paint, and cosmetic industries and in the foodstuff also. It has been estimated that the global consumption of a majority of the natural coloring agents, approximately 70% are derived from *B. orellana* (Thomas *et al.,* 2005). The dyes obtained from the seeds of this plant are now applied on the skin-in the form of makeup and sunscreen, and is also used to prepare body paints, like the paint for lips (lipstick), and on this basis plant is also well-known as the lipstick tree. Bixa leaf extracts have investigated to show a variety of pharmacological assets like antimalarial, antifungal, antibacterial, mutagenic and antimicrobial activities (Mariath *et al.,* 2009; Giorgi *et al.,* 2013).

Leaves of this plant have been utilized in the treatment of several parasitic diseases like malaria and leishmaniasis. Further, the extract from this plant have also been known to show diuretic properties. In order to investigate the diuretic activity of the plant, Soxhlet extraction of the dried leaf powder with petroleum ether, methanol and water were performed in Wister rats by using the standard method. It has been observed that the characteristic diuretic activity of the methanolic extract derived from the leaves of the *B. orellana* not only increased the diuresis *i.e.* urine output but also increased the excretion of ions such as potassium, sodium and chloride (Radhika *et al.,* 2010).

Euphorbia thymifolia (Linn.) Haw. (Euphorbiaceae)

Euphorbia thymifolia is a prostate annual, small branched, pubescent herb. Various parts of this plant such as seeds, leaves as well as the fresh juices derived from the whole plant are employed as an astringent or stimulant in the worm infections. It is also used as a therapeutic drug in many diseases and bowel complaints. In addition to this, it is also utilized as sedative, blood purifier, astringent in diarrhea and dysentery, homeostatic, aromatic, stimulant, demulcent, laxative, anthelminthic, and also in cases of constipation, flatulence, chronic cough; as an antiviral in bronchial paronychia and asthma traditionally (Gabriëlla & Ameenah, 2013; Prasad & Bisht, 2011).

E. thymifolia has been reported for its co-carcinogenic activity which is due to phorbol derivatives, antihyperglycemic, antinociceptive, antioxidant, anti-inflammatory, laxative, anthelmintic, antimicrobial, antibacterial, antifungal and various other actions (Rahmatullah *et al.,* 2012; Nagaraju *et al.,* 2012). The diuretic properties of the *E. thymifolia* crude ethanolic extracts were investigated by the Kane *et al.,* (2009) in albino rats. Subsequently, these rat populations were compared with the furosemide treated rats, a standard drug used in this test (10mg/kg, p.o.). It has been found that the diuretic properties are higher in the fractions of the extract in comparison to the standard drug. Phytoconstituents present in the ethanolic extract of this plant are responsible for the diuretic activities of *E. thymifolia*.

Taraxacum officinale (Linn.) Weber ex F.H. Wigg (Asteraceae)

It is a flowering perennial plant commonly known as dandelion and is commonly used as food. The different parts of this plant especially leaves are consumed in the teas and salads whereas the roots are used as a supernumerary of coffee. In addition, leaves and roots of dandelion have been accomplished to cure joint, kidney, liver and gallbladder complications in humans for hundreds of years (Blumenthal *et al.,* 2000).

Traditionally, cancer and eczema conditions were treated using extracts obtained from the dandelion. Recent studies on mice have been shown that high amounts of

the aqueous extract derived from dandelion leaves shown high diuretic activities comparable to that of furosemide. According to some researchers, it is thought that dandelion has the ability to compensate the potassium loss through diuresis as it possess handsome amount of potassium.

Allium sativum Linn. (Liliaceae)

Garlic is the commonly used name for this plant and is recognized for over 100 distinct phytochemicals and the most significant active compound that gives garlic its pungent smell and health benefit is allicin. The active component allicin, present inn garlic is rich source of sulfur-containing amino acids (Ganjre *et al.,* 2015). A variety of studies have shown that garlic has a potential property of preventing the growth of proliferating cancerous cells and thus its consumption in the food lowers risks of stomach, skin, colon and oral cancers. Pulmonary conditions are also treated with the garlic as it possesses aprodisic, carminative, disinfectant and expectorant properties.

Oils derived from the garlic are a good source of compounds having anthelmintic and rubefacient features. Garlic is also utilized for lowering the blood pressure and cholesterol level, possesses strong antimicrobial activity, help in lipid profile improvement, and boost immune function, along with anti-carcinogenic properties (Rapp, 2017). The natriuretic and biphasic responses of this plant were investigated when the purified fractions of the *A. sativum* were administered intravenously. In the natriuretic responses, it was found that only chloride ions followed the response but potassium ions do not. It was observed that arterial blood pressure and electrocardiogram remained stable. Purified fractions of the garlic suppress the Na+-K+-ATPase in a dose dependent manner. Consequently, it increases the volume of urine *i.e.* diuresis (Pantoja *et al.,* 2000).

MEDICINAL PLANTS AS SOURCES OF ANTIOXIDANTS

Antioxidants are the constituents that have the ability to protect or slow down the damage of the cells caused by the presence of free radicals and are therefore, also referred as scavengers of free-radicals. Free radicals are unstable molecules produced in the body as a result of exposure of harmful chemicals, pollutants, ionizing radiations etc. and these free radicals in the body can damage macromolecules like DNA, RNA, proteins, fats etc. If the genetic material is damaged, it will surely affect the developmental biology of the organism which may have their effect on future generations. However, our body is equipped with well-developed defense system against every problem and for protection of body from free radicals; enzymatic

antioxidant system which includes catalase and glutathione are operational in the body and these are called endogenous antioxidants. Catalase and glutathione work efficiently and help in removal of free radicals from the body. Glutathione peroxidase is more efficient than catalase. In spite of having own well developed antioxidant system, our body still need plant antioxidants due to increase in the likely exposure of the body to the polluted environment that produces free radicals faster as compared to their removal and live example of this case is increase in ageing in the populations which have been revealed in several findings.

Therefore, to boost the body defense system and protect body from free radicals, we need exogenous antioxidants which are obtained from plants or plant-derived products. The inherent abilities of plants to synthesize a variety of antioxidants *viz*., glutathione and ascorbic acid and secondary metabolites such as phenolic compounds possess the ability of preventing the oxidative damage (Kasote *et al.,* 2015).

HISTORICAL BACKGROUND

Terrestrial plants due to their marine adaptation had begun producing antioxidants *viz*., ascorbic acid, tocopherols and polyphenols. Development of many antioxidants occurred, especially during the Jurassic period, as a result of evolution of angiosperms. The development of these antioxidants occurred as chemical defense against the reactive oxygen species (ROS) that are byproducts of photosynthesis (Benzie, 2003). Preservation of dead bodies is a common practice in the ancient Egypt, commonly referred to as 'mummification" and it was achieved by the utilization of the plant's extracts producing handsome amount of phenolic compounds. The earliest evidence of the antioxidants came from the rubber industry in the nineteenth century where they were identified as molecules which have the potential to prevent the degradation or slow down this process and in turn, this allows the effective use of vulcanization process. But now it is known that free radicals and oxygen are involved in the production and use of rubber. Antioxidants are important in the enhancement of the performance of tires (Mattill, 1947).

Several spontaneous reactions were explained which lead to the production of free radicals in the presence of oxygen specifically termed as autoxidation and also some antioxidants were also discovered by the 1940s, which were capable of the breaking chain reactions. It was revealed by the late 1950s that in ageing and in the progression of several diseases, oxidation reactions are involved. Also it was anticipated that these antioxidant molecules prolong the life span by slowing down the ageing process and disease progression (Gutteridge & Halliwell, 2010). The identification and extraction of ascorbic acid from the plants evoked the interest of scientists toward the field of exogenous plant antioxidants (Szent-Giörgyi, 1963).

Antioxidants and Their Role

Free radicals are generated inside the human body or may come across from exogenous sources. In some instances, a condition of imbalance between free radicals and antioxidant activity in the body occurs which is mentioned as oxidative stress which causes damage to cells and tissues. Oxidative stress has been found to be liable for the growth of majority of illnesses and infections (Aruoma, 1994). This free radical production in the body or from outside sources have been found to be liable for the development and progression of various diseases such as cardiovascular and neurodegenerative diseases and their instances have been found to increase with respect to the increased oxidative stress (Kasote *et al.,* 2015).

One of the key ways that help in control of these diseases is the usage of antioxidants. Antioxidants are the inhibitors of oxidation as they have the potential of neutralizing the free radicals in the body. They can be obtained from natural sources as well as artificially. In order to maintain the oxidized state, some of the antioxidants are produced internally such as glutathione and enzymes and others can be obtained from the dietary food sources. They perform various functions in lipid peroxidation which are as follows:

- They decrease the localized concentrations of oxygen in the body.
- They inhibit chain reactions by reducing or inhibiting the initiating radicals.
- They can act as catalysts e.g., metal ions, in order to obstruct the generation of initiating radicals.
- They decompose peroxides to set them free.
- They are the chain breakers and thus help to prevent continued hydrogen abstraction via free radicles.

ANTIOXIDANT POTENTIAL OF PLANTS

Reactive Oxygen Species (ROS) generation occurs at Photosystem I (PS-I) and Photosystem II (PS-II) of the chloroplast, complex-III (ETC) of mitochondria and membrane and matrix of peroxisomes in plants (Gill & Tuteja, 2010). In general, chloroplast, mitochondria and peroxisomes are organelles involved in the ROS generation in plants. The efficient defense system involves enzymatic and non–enzymatic antioxidants that plays significant role in reducing the side effects of these radicals. Glutathione peroxidase, superoxide dismutase, glutathione reductase and catalase comprises the enzymatic antioxidant defense system (Chand & Dave, 2009) while non–enzymatic defense system comprises of glutathione, ascorbic acid, carotenoids, proline etc. and secondary metabolites such as tannins. Within

the stroma and cytosol of the chloroplast, plants biosynthesize the glutathione and ascorbate by using the ultimate electron donor *viz*., NADPH (Alscher *et al.,* 1997). These antioxidants perform various functions in plants for e.g., they act as redox buffers which regulate growth and development of plant by interacting and modulating essential cell processes such as mitosis etc. (Foyer, 2005). Ascorbic acid neutralizes the toxic effects of free radicals as well as helps in regenerating carotenoids and vitamin E which are antioxidant pigments. Glutathione exists in alternative forms *i.e.* it either exists as GSH that is the reduced form or GSSG that is oxidized form. Glutathione reductase enzyme is responsible for the glutathione reduction (Meyer & Hell, 2005). Glutathione presence is essential in the detoxification, antioxidant biochemistry and biosynthetic pathways in plants (Noctor *et al.*, 2012). The free radical production under normal physiological conditions is relatively small (Breusegem & Dat, 2006) but in fluctuating environments, the free radical production increases as a result of which there is an increase in the levels of glutathione (Apel & Hirt, 2004) and decrease in the ratio of GSH to GSSG (Szalai *et al.,* 2009). Phenolic substances which are secondary metabolites also act as antioxidants by detoxifying H_2O_2 and provide protection against UV radiations (Sakihama *et al.,* 2002)

PRESENCE OF ANTIOXIDANTS IN MEDICINAL PLANTS

Approximately two-third of the plant species known around the world have been noted to have the ability to synthesize the antioxidants and antimicrobial compounds and their compounds are used as medicine in traditional medicinal system (Krishnaiah *et al.*, 2011). Medicinal herbs, spices and plants are the source of antioxidants and these antioxidants can be used naturally in crude form. The medicinal plants possessing antioxidant activities belong to a wide range of families such as Zingiberaceae (*Curcuma longa* Linn., *Zingiber officinale* Roscoe), Lamiaceae (*Salvia officinalis* Linn., *Thymus vulgaris* Linn., *Origanum majorana* Linn., *Mentha*, *Ocimum basilicum* Linn., *Melissa officinalis* Linn., and *Salvia rosmarinus* Spenn.), Asteraceae (*Matricaria chamomilla* Linn.), Apiaceae (*Cuminum cyminum* Linn., *Foeniculum vulgare* Mill. and *Carum carvi* Linn.), Myrtaceae (*Eucalyptus oblique* L'Her.) and Ginkgoaceae (*Ginkgo biloba* Linn.) (Škrovánková *et al.,* 2012). Among all, the plant derived compounds, some of them such as phenolics, flavonoids and vitamins are potent antioxidants but only few exogenous antioxidants have been shown to be therapeutically useful (Chand & Dave, 2009). The reason behind this is that these antioxidants interfere with the normal functioning of the physiological and pharmacological processes such as distribution, absorption, metabolism, excretion and storage (Kasote *et al.,* 2015). Still, an inverse relationship has been shown by

various epidemiological studies between the consumption of antioxidants derived from the dietary plant and the pervasiveness of diseases.

Rosmarinus officinalis Spenn. (Lamiaceae)

It is an ever green herb and possess free-radicle scavenging properties due to the presence of compounds such as carnosic acid (Wellwood & Cole, 2004), isorosmanol, carnosol, rosmanol, epirosmanol and rosmarinic acid. The concentration of rosmarinic acid is highest among all the compounds and it is present in all parts of plants. Rosemary extract antioxidant activity depends upon the phenolic composition. Rosemary extracts as well as other extracts from the medicinal plants are commercially used in Europe. These extracts have the ability to inhibit the lipid oxidation (Škrovánková *et al.,* 2012)

Origanum vulgare Linn. (Lamiaceae)

It is a flowering plant and a perennial herb. It also contains rosmarinic acid which is accountable for the antioxidant assets of the plant. In addition, it also contains carnosic acid, flavonoids, and derivatives of phenolic acids and tocopherols. It inhibits lipid peroxidation and great source of antioxidants (Ding et al., 2010).

Asparagus racemosus Willd. (Lamiaceae)

This plant is rich in chemicals such as alkaloids, polyphenols, flavonoids, vitamin C and saponins (shatavarin I-V) all of which have antioxidant activity. It has reduction power as well as it shown the free radical scavenging and other various types of scavenging (Negi et al., 2010).

Thymus vulgaris Linn. (Lamiaceae)

In this plant, various antioxidants are present viz., thymol, carvacrol, rosmarinic acid and flavonoids. Among all of this, antioxidant activity is characterized by the presence of rosmarinic acid and flavonoids. Luteolin and apigenin are the flavonoids present in the thyme. Luteolin is present in high amounts while apigenin is present in small amounts (Justesen & Knuthsen, 2001).

Ocimum basilicum Linn. (Lamiaceae)

Carnosic acid, caffeoyl derivatives and phenolic diterpenes are the potent antioxidants of this plant but rosmarinic acid which is one of the chief phenolic compounds is

liable for the antioxidant actions of basil (Jayasinghe et al., 2003). Basil also contains flavonoids which possess antioxidant activity e.g. catechin (Surveswaran et al., 2007).

Mentha officinalis Linn., Mentha Piperita Linn., *Mentha spicata* Linn. (Lamiaceae)

Mentha piperita and *Mentha spicata* are well known in the genus *Mentha*. Presence of phenolic and flavonoid compounds in the extracts of *Mentha* account for the antioxidant features of this plant (Triantaphyllou et al., 2001). When different species of mint, harvested in two harvest times, were compared for antioxidant actions, it was found that the antioxidant features were higher in July harvest as compared to September harvest (Fialovà et al., 2008).

Melissa officinalis Linn. (Lamiaceae)

Carnosic acid, triterpene acids, ursolic and oleanolic acids are the major antioxidants of the balm (Herodež *et al.,* 2003). The extracts prepared in methanol, water and ethanol of this plant have the potential to lessen the damage of the various cells as well as tissues caused by the presence or exposure to free radicals that persuade oxidative stress and lipid peroxidation (Pereira *et al.,* 2009).

Cuminum cyminum Linn. (Apiaceae)

Flavonoids, coumarins and phenolic acids are the antioxidants present in different parts of Cumin. Different parts of this plant such as flowers, leaves, stems and roots are used for making the cumin oils. The antioxidant components of cumin oil are γ -terpinene, α-terpinene, and bornyl acetate (Bettaieb *et al.*, 2010). The latency of these antioxidants is to retard the production of free radicals that are scavenging and ultimately inhibit the lipid peroxidation (Thippeswamy & Naidu, 2005). There are various varieties of cumin but the bitter cumin possesses the highest level of phenolics and is efficient in the inhibition of oxidation (Ani *et al.,* 2006).

Foeniculum vulgare Mill. (Apiaceae)

It is a flowering plant as well as perennial herb with yellow flowers. Trans-anethol, fenchone, estragole, and limonene are the compounds present in the oil extract from fennel and because of which it shows potent antioxidant activity. The antioxidants present in this plant generally belongs to the phenolic acids and flavonols, flavones are derivatives of hydroxycinnamic acid with their glycosides mainly coumarins (Surveswaran *et al.,* 2007).

Carum carvi Linn. (Apiaceae)

Meridian fennel or Persian cumin is the pet names of this plant. Thymol, carvacrol, and flavonoids are the antioxidant compounds present in this biennial herb. The extracts prepared from the caraway possess the ability of chelating the free radicals as well as they prevent the triglyceride peroxidation (Bamdad *et al.*, 2006).

Curcuma longa Linn. (Zingiberaceae)

Curcuma longa is very common in the Indian houses as the powder of turmeric is used for various purposes such as in cooking. It also possesses medicinal properties. It is also used as an antiseptic. Phenolic compounds, curcumin, bisdemethoxycurcumin, and demethoxycurcum, p-coumaric acid and ferulic acid are present in the turmeric and all of them show potent antioxidants properties (Kumar *et al.,* 2006).

Zingiber officinale Roscoe (Zingiberaceae)

Zingiber officinale is widely used in the households in both dry as well as in fresh forms. It is used in Chinese medicines, Ayurveda, Siddha and Unani. Various problems of body such as osteo- and rheumatoid arthritis, diabetes mellitus, vomiting, gastritis, nausea and disorders of the heart has been treated by the use of ginger. Ginger is a major herbal rejuvenator or kaya karpam supported due to its multiple biological properties (Bhattacharya & Muruganandam, 2003). Ginger contains gingerol-related compounds such as gingerols, shogaols, gingediols, zingerone, dehydrozingerone etc. which have the antioxidant activity (Surveswaran *et al.,* 2007; Tao *et al.,* 2008).

Cocculus hirsutus (Linn.) Diels (Zingiberaceae)

The ethanol extract derived from the aerial parts of *C. hirsutus* have been found to be directed against a wide range of radicals such as superoxide, 1,1-diphenyl–2-picrylhydrazyl, hydroxyl radicals, and nitric oxide. The extract comprises of antioxidant vitamins and phenolic compounds which are responsible for the characterized antioxidant nature of the extract (Panda *et al.,* 2011).

Withania somnifera (L.) Dunal (Zingiberaceae)

Indian Ginseng is the common name of *W. somnifera* as its medicinal value is comparable to Ginseng which is famous for improving the stress conditions. The tuberous roots of *W. somnifera* plants are the hub of different medicinal properties.

The extracts prepared from the roots of the plant are known to have anticancer, anti-inflammatory and antioxidant properties (Udayakumar *et al.,* 2010).

Azardirachta indica A. Juss. (Zingiberaceae)

In India, people traditionally utilized different parts of the plant and medicines prepared from them for treating various diseases and ailments and some people consider it as a holy plant and pray it. The leaves, roots, seeds and flowers of this holy plant have different medicinal values. Various studies have shown that different parts of this plant or compounds obtained from them possess antimicrobial, anti-inflammatory, analgesic, antidiabetic, immune-modulatory, antioxidant and anticancer properties and still are used for treating various illnesses (Wolinsky *et al.,* 1996; Zhang *et al.,* 2010).

Ginkgo biloba Linn. (Ginkgoaceae)

It is also known as maidenhair tree. It is rich in antioxidants like coumarins, catechin hydrate, rutin, and quercetin, and because of these constituents, ginkgo shows good antioxidant activity (Maltas & Yildiz, 2012). Essential oils obtained from this also contain antioxidants such as cumin aldehyde, cuminal, and safranal.

Matricaria chamomilla (Linn.) Rydb (Asteraceae)

The name chamomile is used for various daisy like plants and both the species possess medicinal values. The essential oils prepared from chamomile possess significant antioxidant characteristics and the compounds liable for these activities are sesquiterpenes, and some monoterpenes (Costescu *et al.,* 2008).

Eucalyptus globulus Labill. (Myrtaceae)

The extracts from this plant contain several compounds *viz*., hydrolysable tannin dimer, ellagic acid, polyphenol, oenothein B, and gallic acid etc. and all these are responsible for antioxidant activity of the eucalyptus. The extract prepared from the leaves of this plant also possesses antioxidant activities. The extract contains the compound 3-O-β-D-glucuronide of quercetin and kaempferol which possess the antioxidant activity (Amakura *et al.*, 2009). They possess the ability of scavenging free radicals.

Annona squamosal Linn. (Myrtaceae)

The common name of *A. squamosal* is Custard apple or Sitaphal. The presence of flavonoids in this plant confers the ability to destroy or reduce the free radicals. Moreover, these compounds shown a significant increase in the activity of antioxidant enzymes. Further, it plays a role in inhibition of lipid peroxidation (Kaleen *et al.,* 2006).

Glycyrrhiza glabra Linn. (Myrtaceae)

A variety of compounds have been reported from this plant which possess the antioxidant activities which include glycyrrhizin, flavones and coumarins. The antioxidant properties of this plant were identified in a study on rats. In this study, it was observed that extracts prepared from the plant reduced the generation of free radicals as a result of which lipid peroxidation is inhibited in the liver microsomes of rat (Naik & Satav, 2003).

Camellia sinensis (Linn.) Kuntze (*Myrtaceae*)

It is an evergreen shrub and is commonly known as tea tree. From this plant, different varieties of tea are obtained such as black tea, white tea, yellow tea, green tea etc. Among all of them, green tea is to be a potent inhibitor of oxidation due to its antioxidant properties. Green tea is most widely consumed beverage in worldwide (Naik *et al.,* 2009). It also possesses anticancer activities. It contains polyphenols as well as phenolic compounds such as gallic acid, gallocatechin, catechin, epicatechin, epigallocatechin, epicatechingallate etc. which are responsible for its antioxidant as well as anticancer activities.

CONCLUSION

Now-a-days, use of alternative or complementary medicines which are also known by the name of new-age medicines are becoming a trend in this new age of science and technology as a result of which they are providing enormous opportunities for the development of natural medicines or herbal medicines. Traditional medicinal systems have been well known from the ancient times in many countries of Asian subcontinent. This is an advantageous situation for these countries as they are able to gain significant knowledge from the intelligence of traditional practitioners. Moreover, ethno-botanical knowledge of the past and present people is worthwhile in the development of safer and cost effective drugs. Very much understanding of

the mechanism and action of these compounds known to exhibit antioxidant and diuretic activities came from the earlier studies. They are major source of natural products which can have either antioxidants or antimicrobial actions in nature. Due to increasing side effects of using synthetic diuretic and antibiotics, we need to be directed towards the plant derived drugs with minimal adverse effects. Diuretics are, nowadays, used in the primary treatment of hypertensive patients. Diuretics prepared from the herbs either have no or less adverse effect as compared to the allopathic medicines. Antioxidants are important as they have the ability to prevent the DNA damage from the free radicals, generating inside the body in metabolic reactions or by exposing to UV lights as well as increase longevity. The basis of the antioxidant activity of these compounds is the redox potential which allows them to be acted as hydrogen donors, metal chelators and reducing agents etc. These compounds have the tendency to break the free radical chain reactions either by donating an atom of hydrogen or by inhibiting the peroxide formation. However, this action is accomplished in the presence of the reductants. On the basis of the above said knowledge, it could be concluded that plants are the hub of compounds having enormous properties *viz*., anti-inflammatory, antioxidants, diuretics, antibacterial etc. which can be exploited for the development of new age medicines. This is a crucial step in the establishment of those medicine which are free from side effects in comparison to other drugs and medicines.

REFERENCES

Alscher, R. G., Donahue, J. L., & Cramer, C. L. (1997). Reactive oxygen species and antioxidants: Relationships in green cells. *Physiologia Plantarum*, *100*(2), 224–233. doi:10.1111/j.1399-3054.1997.tb04778.x

Amakura, Y., Yoshimura, M., Sugimoto, N., Yamazaki, T., & Yoshida, T. (2009). Marker constituents of the natural antioxidant *Eucalyptus* leaf extract for the evaluation of food additives. *Bioscience, Biotechnology, and Biochemistry*, *73*(5), 1060–1065. doi:10.1271/bbb.80832 PMID:19420705

Ani, V., Varadaraj, M. C., & Naidu, K. A. (2006). Antioxidant and antibacterial activities of polyphenolic compounds from bitter cumin (*Cuminum nigrum* L.). *European Food Research and Technology*, *224*(1), 109–115. doi:10.100700217-006-0295-z

Anonymous. (2005). *The Wealth of India-Raw Materials*. New Delhi: Council of Scientific and Industrial Research.

Apel, K., & Hirt, H. (2004). Reactive oxygen species: Metabolism, oxidative stress, and signal transduction. *Annual Review of Plant Biology*, *55*(1), 373–399. doi:10.1146/annurev.arplant.55.031903.141701 PMID:15377225

Archana, N. P., & Anita, A. M. (2006). A study on clinical efficacy of *Lepidium sativum* seeds in treatment of bronchial asthma. *Iranian Journal of Pharmacology and Therapeutics*, *5*, 55–59.

Aruoma, O. I. (1994). Nutrition and health aspects of free radicals and antioxidants. *Food and Chemical Toxicology*, *32*(7), 671–683. doi:10.1016/0278-6915(94)90011-6 PMID:8045480

Bamdad, F., Kadivar, M., & Keramat, J. (2006). Evaluation of phenolic content and antioxidant activity of Iranian caraway in comparison with clove and BHT using model systems and vegetable oil. *International Journal of Food Science & Technology*, *41*(s1), 20–27. doi:10.1111/j.1365-2621.2006.01238.x

Baquar, S. R. (1989). *Medicinal and Poisonous Plants of Pakistan*. Karachi, Pakistan: Printas.

Barrar, F. S. K. (2003). *Text book of pharmacology*. New Delhi: S. Chand.

Benzie, I. F. F. (2003). Evolution of dietary antioxidants. *Comparative Biochemistry and Physiology. Part A, Molecular & Integrative Physiology*, *136*(1), 113–126. doi:10.1016/S1095-6433(02)00368-9 PMID:14527634

Bettaieb, I., Bourgou, S., Wannes, W. A., Hamrouni, I., Limam, F., & Marzouk, B. (2010). Essential oils, phenolics, and antioxidant activities of different parts of cumin (*Cuminum cyminum* L.). *Journal of Agricultural and Food Chemistry*, *58*(19), 10410–10418. doi:10.1021/jf102248j PMID:20809647

Bhattacharya, S. K., & Muruganandam, A. V. (2003). Adaptogenic activity of *Withania somnifera:* An experimental study using a rat model of chronic stress. *Pharmacology, Biochemistry, and Behavior*, *75*(3), 547–555. doi:10.1016/S0091-3057(03)00110-2 PMID:12895672

Blumenthal, M., Goldberg, A., & Brinckmann, J. (2000). *Herbal Medicine. Expanded Commission E monographs*. Integrative Medicine Communications.

Breusegem, F. V., & Dat, J. F. (2006). Reactive oxygen species in plant cell death. *Plant Physiology*, *141*(2), 384–390. doi:10.1104/pp.106.078295 PMID:16760492

Chand, S., & Dave, R. (2009). *In vitro* models for antioxidant activity evaluation and some medicinal plants possessing antioxidant properties: An overview. *African Journal of Microbiological Research*, *3*, 981–996.

Costescu, C. I., Hădărugă, N. G., Rivis, A., Hădărugă, D. I., Lupea, A. X., & Pârvu, D. (2008). Antioxidant activity evaluation of some *Matricaria chamomilla* L. extracts. *Journal of Agroalimentary Processes and Technologies*, *14*, 417–432.

Datir, S. B., Ganjare, A. B., Nirmal, S. A., Bhawar, S. B., Bharati, D. K., & Patil, M. J. (2009). Evaluation of antiallergic activity of the various extracts of the aerial part of *Achyranthes aspera* var. *Porphyristachya* (wall. Ex moq.) Hook. f. *Pharmacologyonline*, *3*, 921–925.

Dhale, D. A., & Bhoi, S. (2013). Pharmacognostic Characterization and Phytochemical Screening of *Achyranthes aspera* Linn. *Current Agriculture Research Journal*, *1*(1), 51–57. doi:10.12944/CARJ.1.1.07

Ding, H. Y., Chou, T. H., & Liang, C. H. (2010). Antioxidant and antimelanogenic properties of rosmarinic acid methyl ester from *Origanum vulgare. Food Chemistry*, *123*(2), 254–262. doi:10.1016/j.foodchem.2010.04.025

Duke, J. A., Bogenschutz-Godwin, M. J., Ducelliar, J., & Duke, P. A. K. (2002). *Handbook of Medicinal Herbs*. Boca Raton, FL: CRC Press. doi:10.1201/9781420040463

Elias, M. E. A., Schroth, G., Macêdo, J. L. V., Mota, M. S. S., & Angelo, S. A. (2002). Mineral nutrition, growth and yields of annatto trees (*Bixa orellana*) in agroforestry on an Amazonian Ferralsol. *Experimental Agriculture*, *38*(3), 277–289. doi:10.1017/S0014479702003034

Fialová, S., Tekel'ová, D., Mrlianová, M., & Grančai, D. (2008). The determination of phenolics compounds and antioxidant activity of mints and balms cultivated in Slovakia. *Acta Facultatis Pharmaceuticae Universitatis Comenianae*, *55*, 96–102.

Foyer, C. H., & Noctor, G. (2005). Redox homeostasis and antioxidant signaling: A metabolic interface between stress perception and physiological responses. *The Plant Cell*, *17*(7), 1866–1875. doi:10.1105/tpc.105.033589 PMID:15987996

Gabriëlla, H.S. & Ameenah, G.F. (2013). *Medicinal Plants Plant Resources of Tropical Africa (Program)*. Academic Press.

Ganjre, A., Kathariya, R., Bagul, N., & Pawar, V. (2015). Anti-carcinogenic and antibacterial properties of selected spices: Implications in Oral Health. *Clinical Nutrition Research*, *4*(4), 209–215. doi:10.7762/cnr.2015.4.4.209 PMID:26566515

Gill, S. S., & Tuteja, N. (2010). Reactive oxygen species and antioxidant machinery in abiotic stress tolerance in crop plants. *Plant Physiology and Biochemistry*, *48*(12), 909–930. doi:10.1016/j.plaphy.2010.08.016 PMID:20870416

Giorgi, A., De Marinis, P., Granelli, G., Chiesa, L. M., & Panseri, S. (2013). Secondary metabolite profile, antioxidant capacity, and mosquito repellent activity of *Bixa orellana* from Brazilian Amazon region. *Journal of Chemistry*. *Article ID*, *409826*, 1–10.

Gutteridge, J. M. C., & Halliwell, B. (2010). Antioxidants: Molecules, medicines and myths. *Biochemical and Biophysical Research Communications*, *393*(4), 561–564. doi:10.1016/j.bbrc.2010.02.071 PMID:20171167

Herodež, Š. S., Hadolin, M. Š., Škerget, M., & Knez, Ž. (2003). Solvent extraction study of antioxidants from balm. *Food Chemistry*, *80*(2), 275–282. doi:10.1016/S0308-8146(02)00382-5

Jayasinghe, C., Gotoh, N., Aoki, T., & Wada, S. (2003). Phenolics composition and antioxidant activity of sweet basil (*Ocimum basilicum* L.). *Journal of Agricultural and Food Chemistry*, *51*(15), 4442–4449. doi:10.1021/jf034269o PMID:12848523

Justesen, U., & Knuthsen, P. (2001). Composition of flavonoids in fresh herbs and calculation of flavonoid intake by use of herbs in traditional Danish dishes. *Food Chemistry*, *73*(2), 245–250. doi:10.1016/S0308-8146(01)00114-5

Kaleen, M., Asif, M., Ahmed, Q. U., & Bano, B. (2006). Antidiabetic and Antioxidant activity of *Annona squamosa* extract in streptorotocin induced diabetic rats. *Singapore Medical Journal*, *47*, 670–675. PMID:16865205

Kane, S. R., Apte, V. A., Todkar, S. S., & Mohite, S. K. (2009). Diuretic and laxative activity of ethanolic extract and its fractions of *Euphorbia thymifolia* Linn. *International Journal of Chemical Technology Research*, *1*, 149–152.

Kasote, D. M., Katyare, S. S., Hegde, M. V., & Bae, H. (2015). Significance of antioxidant potential of plants and its relevance to therapeutic applications. *International Journal of Biological Sciences*, *11*(8), 982–999. doi:10.7150/ijbs.12096 PMID:26157352

Kloos, H. (1976). Preliminary studies of medicinal plants and plant products in Ethiopian markets. *Journal of Ethiopian Pharmaceutical Association*, *2*, 18–28.

Kokko, P. J. (1984). Site and mechanism of action of diuretics. *The American Journal of Medicine*, *77*(5), 11–17. doi:10.1016/S0002-9343(84)80003-0 PMID:6496555

Krishnaiah, D., Sarbatly, R., & Nithyanandam, R. (2011). A review of the antioxidant potential of medicinal plant species. *Food and Bioproducts Processing*, *89*(3), 217–233. doi:10.1016/j.fbp.2010.04.008

Kumar, G. S., Nayaka, H., Dharmesh, S. M., & Salimath, P. V. (2006). Free and bound phenolic antioxidants in amla (*Emblica officinalis*) and turmeric (*Curcuma longa*). *Journal of Food Composition and Analysis*, *19*(5), 446–452. doi:10.1016/j.jfca.2005.12.015

Lipschitz, W. L., Hadidian, Z., & Kerpcsar, A. (1943). Bioassay of diuretics. *The Journal of Pharmacology and Experimental Therapeutics*, *79*, 97–110.

Maltas, E., & Yildiz, S. (2012). Evaluation of phytochemicals and antioxidant activity of *Ginkgo biloba* from Turkey. *Pharmacology*, *3*, 113–120.

Mariath, I. R., Falcão, H. S., Barbosa-Filho, J. M., Sousa, L. C. F., Tomaz, A. C. A., Batista, L. M., ... Cunha, E. V. L. (2009). Plants of the American continent with antimalarial activity. *Revista Brasileira de Farmacognosia*, *19*(1a), 158–191. doi:10.1590/S0102-695X2009000100026

Mattill, H. A. (1947). Antioxidants. *Annual Review of Biochemistry*, *16*(1), 177–192. doi:10.1146/annurev.bi.16.070147.001141 PMID:20259061

Meyer, A. J., & Hell, R. (2005). Glutathione homeostasis and redox-regulation by sulfhydryl groups. *Photosynthesis Research*, *86*(3), 435–457. doi:10.100711120-005-8425-1 PMID:16315075

Nagaraju, G., Chinnalalaiah, R., Nagaraju, P., & Kumar, P. A. (2012). Anti-inflammatory and anti-oxidant activities of ethanolic extract of *Euphorbia thymifolia* Linn. Whole plant. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*, 516–519.

Naik, D. G., Vaidya, H. S., & Behera, B. C. (2009). Antioxidant activity of Indian propolis. *Journal of ApiProduct and ApiMedical Science*, *1*(4), 110–120. doi:10.3896/IBRA.4.01.4.03

Naik, G. H., & Satav, J. G. (2003). Comparative antioxidant activity of individual herbal components used in Ayurvedic medicine. *Phytochemistry*, *63*(1), 97–104. doi:10.1016/S0031-9422(02)00754-9 PMID:12657303

Negi, J. S., Singh, P., Joshi, G. P., Rawat, M. S., & Bisht, V. K. (2010). Chemical constituents of Asparagus. *Pharmacognosy Reviews*, *4*(8), 215. doi:10.4103/0973-7847.70921 PMID:22228964

Noctor, G., Mhamdi, A., Chaouch, S., Han, Y., Neukermans, J., Marquez-Garcia, B., ... Foyer, C. H. (2012). Glutathione in plants: An integrated overview. *Plant, Cell & Environment*, *35*(2), 454–484. doi:10.1111/j.1365-3040.2011.02400.x PMID:21777251

Panda, B. R., Mohanta, S. R., Manna, A. K., & Si, S. (2011). *In vitro* antioxidant activity on the aerial parts of *Cocculus hirsutus* Diels. *Journal of Advanced Pharmaceutical Research*, *2*, 18–23.

Pantoja, C. V., Martín, N. T., Norris, B. C., & Contreras, C. M. (2000). Purification and bioassays of a Diuretic and natriuretic fraction from garlic (*Allium sativum*). *Journal of Ethnopharmacology*, *70*(1), 35–40. doi:10.1016/S0378-8741(99)00145-2 PMID:10720787

Patel, U., Kulkarni, M., Undale, V., & Bhosale, A. (2009). Evaluation of diuretic activity of aqueous and methanol extracts of *Lepidium sativum* Garden Cress (Cruciferae) in Rats. *Tropical Journal of Pharmaceutical Research*, *8*(3), 215–219. doi:10.4314/tjpr.v8i3.44536

Paul, D., De, D., Ali, K. M., Chatterjee, K., Nandi, D. K., & Ghosh, D. (2010). Comparative study on the spermicidal activity of organic solvent fractions from hydroethanolic extracts of *Achyranthes aspera* and *Stephania hernandifolia* in human and rat sperm. *Contraception*, *81*(4), 355–361. doi:10.1016/j.contraception.2009.09.001 PMID:20227555

Pereira, R. P., Fachinetto, R., de Souza Prestes, A., Puntel, R. L., Santos da Silva, G. N., Heinzmann, B. M., ... Rocha, J. B. T. (2009). Antioxidant effects of different extracts from *Melissa officinalis, Matricaria recutita* and *Cymbopogon citratus. Neurochemical Research*, *34*(5), 973–983. doi:10.100711064-008-9861-z PMID:18853256

Prasad, K., & Bisht, G. (2011). Evaluation of nutritive minerals and antioxidants values of *Euphorbia thymifolia* Linn. *Current Research in Chemistry*, *3*(2), 98–105. doi:10.3923/crc.2011.98.105

Radhika, B., Nasreen, B., Srisailam, K., & Reddy, V. M. (2010). Diuretic activity of *Bixa orellana* Linn. leaf extracts. *Indian Journal of Natural Products and Resources*, *1*, 353–355.

Rahmatullah, M., Hasan, S. K., Ali, Z., Rahman, S., & Jahan, R. (2012). Antihyperglycemic and antinociceptive activities of methanolic extract of *Euphorbia thymifolia* L. whole plants. *Journal of Chinese Integrative Medicine*, *10*(2), 228–232. doi:10.3736/jcim20120213 PMID:22313890

Rapp, C. (2007). *Clove as effective as topical anesthetic*. Herbal Gram.

Sakihama, Y., Cohen, M. F., Grace, S. C., & Yamasaki, H. (2002). Plant phenolic antioxidant and prooxidant activities: Phenolics-induced oxidative damage mediated by metals in plants. *Toxicology*, *177*(1), 67–80. doi:10.1016/S0300-483X(02)00196-8 PMID:12126796

Sangmai, T. K., Meitei, U. D., Sanjenbam, R., & Khumbongmayum, S. (2010). Diuretic property of aqueous extract of leaves of *Mimosa pudica* Linn on experimental albino rats. *Journal of Natural Products*, *3*, 173–178.

Shree Devi, M. S. (2011). Acute toxicity and diuretic activity of *Mangifera indica* Linn bark extracts. *International Journal of Pharmacology and Biosciences*, *2*, 141–146.

Škrovánková, S., Mišurcová, L., & Machů, L. (2012). Antioxidant activity and protecting health effects of common medicinal plants. *Advances in Food and Nutrition Research*, *67*, 75–139. doi:10.1016/B978-0-12-394598-3.00003-4 PMID:23034115

Srivastav, S., Singh, P., Mishra, G., Jha, K. K., & Khosa, R. L. (2011). *Achyranthes aspera* an important medicinal plant: A review. *Journal of Natural Product and Plant Resources*, *1*, 1–14.

Surveswaran, S., Cai, Y. Z., Corke, H., & Sun, M. (2007). Systematic evaluation of natural phenolic antioxidants from 133 Indian medicinal plants. *Food Chemistry*, *102*(3), 938–953. doi:10.1016/j.foodchem.2006.06.033

Szalai, G., Kellos, T., Galiba, G., & Kocsy, G. (2009). Glutathione as an antioxidant and regulatory molecule in plants under abiotic stress conditions. *Journal of Plant Growth Regulation*, *28*(1), 66–80. doi:10.100700344-008-9075-2

Szent-Giörgyi, A. (1963). Lost in the twentieth century. *Annual Review of Biochemistry*, *36*(1), 1–15. doi:10.1146/annurev.bi.32.070163.000245 PMID:14140702

Tao, Q. F., Xu, Y., Lam, R. Y. Y., Schneider, B., Dou, H., Leung, P. S., ... Zhao, Y. (2008). Diary heptanoids and a monoterpenoid from the rhizomes of *Zingiber officinale*: Antioxidant and cytoprotective properties. *Journal of Natural Products*, *71*(1), 12–17. doi:10.1021/np070114p PMID:18177011

Thippeswamy, N. B., & Naidu, K. A. (2005). Antioxidant potency of cumin varieties-Cumin, black cumin and bitter cumin-On antioxidant systems. *European Food Research and Technology*, *220*(5-6), 472–476. doi:10.100700217-004-1087-y

Thippeswamy, N. B., & Naidu, K. A. (2005). Antioxidant potency of cumin varieties—cumin, black cumin and bitter cumin—on antioxidant systems. *European Food Research and Technology*, *220*(5-6), 472–476. doi:10.100700217-004-1087-y

Thomas, E. P., Colvin, M., Rosen, S. B., Zuccarini, C., & Petzer, S. (2005). *HIV prevalence study and costing analysis undertaken for the development of an HIV/AIDS workplace strategy for Buffalo City Municipality*. Medical Research Council.

Triantaphyllou, K., Blekas, G., & Boskou, D. (2001). Antioxidative properties of water extracts obtained from herbs of the species Lamiaceae. *International Journal of Food Sciences and Nutrition*, *52*, 313–317. doi:10.1080/09637480120057512 PMID:11474895

Udayakumar, R., Kasthurirengan, S., Vasudevan, A., Mariashibu, T. S., Rayan, J. J., Choi, C. W., ... Kim, S. C. (2010). Antioxidant effect of dietary supplement *Withania somnifera* L. reduces blood glucose levels in alloxan-induced diabetic rats. *Plant Foods for Human Nutrition (Dordrecht, Netherlands)*, *65*(2), 91–98. doi:10.100711130-009-0146-8 PMID:20186490

Wellwood, C. R. L., & Cole, R. A. (2004). Relevance of carnosic acid concentrations to the selection of rosemary, *Rosmarinus officinalis* (L.), accessions for optimization of antioxidant yield. *Journal of Agricultural and Food Chemistry*, *52*(20), 6101–6107. doi:10.1021/jf035335p PMID:15453673

Wolinsky, L. E., Mania, S., Nachnani, S., & Ling, S. (1996). The inhibiting effect of aqueous *Azadirachta indica* (Neem) extract upon bacterial properties influencing in vitro plaque formation. *Journal of Dental Research*, *75*(2), 816–822. doi:10.1177/00220345960750021301 PMID:8655780

Zafar, R. (2009). *Medicinal Plants of India*. CBS Publishers and Distributors.

Zahir, A. A., Rahuman, A. A., Kamaraj, C., Bagavan, A., Elango, G., Sangaran, A., & Kumar, B. S. (2009). Laboratory determination of efficacy of indigenous plant extracts for parasites control. *Parasitology Research*, *105*(2), 453–461. doi:10.100700436-009-1405-1 PMID:19308453

Zhang, Y. Q., Xu, J., Yin, Z. Q., Jia, R. Y., Lu, Y., Yang, F., ... Yi, G. (2010). Isolation and identification of the antibacterial active compound from petroleum ether extract of neem oil. *Fitoterapia*, *81*(7), 747–750. doi:10.1016/j.fitote.2010.03.015 PMID:20362038

Chapter 5
Current Update on Natural Agents Against Triple Negative Breast Cancer

Prathibha Sivaprakasam
B. S. Abdur Rahman Crescent Institute of Science and Technology, India

Sureshkumar Anandasadagopan
https://orcid.org/0000-0001-5178-005X
Central Leather Research Institute, India

Tamilselvi Alagumuthu
Central Leather Research Institute, India

Ashok Kumar Pandurangan
https://orcid.org/0000-0003-2824-1757
B. S. Abdur Rahman Crescent Institute of Science and Technology, India

ABSTRACT

Breast cancer (BC) is sub-categorized into several well-recognized subtypes including estrogen receptor (ER), progesterone receptor (PR), and HER2 triple-negative breast cancer (TNBC). It is a heterogeneous disease entity constituting about 15% of breast cancer cases worldwide. TNBC is associated with poor prognosis and lack of sustained response to conventional chemotherapeutic agents. Although no approved targeted therapy is available for TNBCs, molecular-profiling efforts have revealed promising molecular targets such as the Wnt/β-catenin, STAT3, VEGF,

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EGFR, polyadenosine ribose polymerase inhibitors (PARPi) and DNA repair pathway, androgen pathway, and NOTCH pathway. Moreover, more research needs to be performed in the area of TNBC aiming at dissecting potential pathways and identifying potential molecular signatures to develop new targeted biologic modifiers. Natural agents are the abundant chemical compounds available from diverse plants. The authors aimed to summarize the current evidence and discuss the natural agents that target TNBC using different pathways.

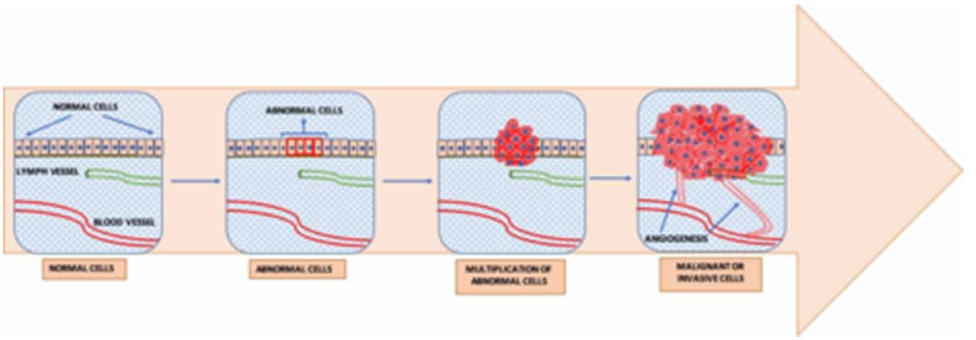
INTRODUCTION

Cancers can be precisely defined as an abnormal growth of cells which are usually derived from a single aberrant cell. These cancerous cells tend to lose their normal control mechanisms and multiplies incessantly to form a multitude of cancerous tissue called tumor which besieges the nearby tissues, traverses to varied regions of the body from the primary site (metastasis) and promotes growth of new blood vessels from which the cells procure nutrients (Pandurangan *et al*., 2015).

In short, cancer is the chaotic proliferation of cells with the following eminent features - lack of differentiation of cells, local seizure of tissues in proximity and metastasis. Tumors can either be malignant or benign. Benign tumors are restricted to one area and do not metastasize. Whereas, malignant tumors, made up of cancerous cells can easily metastasizes within the body by traversing through the bloodstream or lymphatic system (lymph fluid).

Amidst greater than 100 different cancer types, most cancers derive their name from the site of origin in the body. For instance, lung cancer begins from the lungs and breast cancer is triggered from the breasts.

Figure 1. Understanding breast cancer



BREAST CANCER (BC)

Aetiology

The most classical and familiar cancer amongst women is Breast Cancer (BC) and it is also confirmed to be the second most common reason for cancer associated mortality in women (Angahar, 2017). A statistical study in 2015 reported that each year nearly 1,384,155 new patients were registered around the globe with approximately 459,000 linked deaths per annum (Tao *et al*., 2015). Nearly 198,000 cancer related deaths occur annually which signifies nearly 15.4% of the total mortality rate in the developed regions alone succeeding lung cancer (Ly *et al*., 2011). BC is an extensively diversified form of cancer pertaining to its pathological characteristics exhibiting passive growth and eminent prognosis in some while others displaying aggressiveness. According to recent predictions and statistics conducted worldwide, BC and its linked mortality are found to be spiralling. GLOBOCAN statistical reports of the year 2012 reveals that, proximately 1.7 million women were detected with BC and close to 522,000 linked deaths had occurred which eventually signifies increased BC incidence and its linked deaths by nearly 18% since 2008. Another study by the American Cancer Society states that one among every eight women between the age group of 40 to 59 in the United States possess the chance of developing BC in her lifetime (Cox & Morgan, 2013). It has also been anticipated that the incidence of female BC worldwide may reach nearly 3.2 million new cases per annum by the year 2050 (Tao *et al*., 2015) and that the lifetime risk of a woman to develop the invasive form of BC will reach approximately 12.6%.

Breast Cancer Subtypes

BC is a multitudinous aggregation of diseases. BC has many subtypes with prominent biological characteristics and variations in response patterns to several treatment modalities and clinical consequences (Yersal & Barutca, 2014). Based on the gene expression profile demonstrated through immunohistochemical surrogate panel the molecular subtypes of BC are classified as follows: luminal A (PR and/or ER positive & less than 14% Ki-67 expression), luminal B (PR and/or ER positive & greater than14% Ki-67 expression), luminal/HER2 (PR and/or ER positive & HER2 positive), HER2 enriched (PR and ER negative & HER2 positive) and basal-like (PR and ER negative, HER2 negative & EGFR and/or CK5/6 positive). A distinct class of tumour called the Triple-negative (TN) tumours are those that do not exhibit EGFR or CK5/6 and are contemplated to be TN non-basal (Pandurangan & Mustafa, 2018).

- **Luminal A**: This cancer sub-type is positive for both the hormone-receptors (progesterone and/or estrogen), HER2 negative and exhibits minimal Ki-67 protein levels, eventually controlling cancer cell growth. They are characterised by best prognosis along with low-grade and slow growing features.
- **Luminal B:** This type of cancer is positive for hormone-receptors progesterone and/or estrogen but either positive or negative for HER2 with elevated expressions of Ki-67. They exhibit marginally accelerated growth than the luminal A cancers, however, they only have a moderate rate of prognosis.
- **Triple-Negative/Basal-Like:** This cancer type is negative for all hormone-receptors – estrogen, progesterone and HER2. It is more widespread in younger women, *BRCA1* gene mutations harbouring women and also among African-American origin women.
- **HER2-Enriched:** This cancer type is negative for the hormone-receptors progesterone and estrogen but positive for HER2. This HER2-accomplished cancer multiplies at a much-augmented pace in comparison to the luminal cancers exhibiting poor prognosis, however, the HER2 protein specific 'targeted therapies' have shown promising results.
- **Normal-Like:** This type of cancer is similar to the luminal A type, i.e., they are positive for the hormone receptors progesterone and/or estrogen and negative for HER2. However, the diminished Ki-67protein levels controls the proliferation of cancer cells. They exhibit good prognosis yet faintly less than that of the luminal A cancer's prognosis.

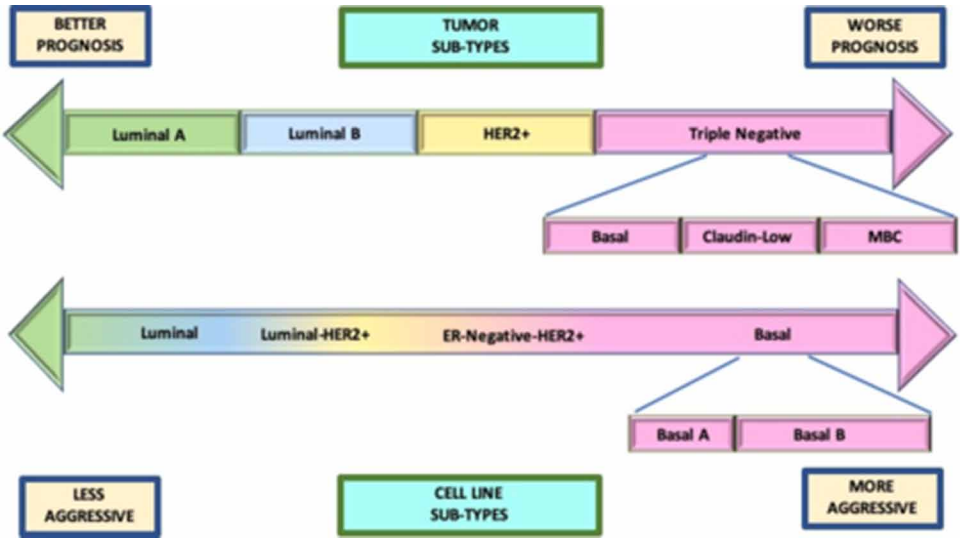
Young women form a special group in BC cases with evidence suggesting a later stage presentation with more aggressive tumours. They are generally characterized by a high incidence of hormone negative tumours where TNBC is more common and also the 5-year disease-free survival (DFS) aspect is significantly worse (Hariharan & Rao, 2019).

Triple Negative Breast Cancer (TNBC)

TNBC is devoid of progesterone receptors, estrogen Receptors and excess HER2 protein suggesting that this cancer type is not altered by estrogen and progesterone or the HER2 protein. Almost, 10-20% of the BC cases are TNBCs, which are aggressive in nature, exhibit poor prognosis and do not have effective response to hormone therapies or drugs that specifically act against the receptors of HER2 protein (Pandurangan & Mustafa, 2018). Systemic treatment alternatives for the metastatic form of TNBC (mTNBC) are restricted to cytotoxic chemotherapeutic agents which have lesser response rates.

TNBC is predominantly immunogenic amongst other breast cancer subtypes. The tumour-infiltrating lymphocytes play a crucial part in both prognosis and prediction of TNBC. Also, Programmed Cell Death-Ligand 1 (PD-L1) expression is higher in TNBC patients. It is also characterized by advanced highly developed stage of the tumour, remarkably greater metastatic rates, greater histologic grade and greater proliferative index (measured by the mitotic account or the proliferative index of Ki-67).

Figure 2. Breast cancer sub-types



Another added feature of TNBC is its relapse between 1 and 3 years after diagnosis and also the incidence of large number of deaths within 5 years of treatment when compared to the non-TNBC phenotypes. TNBC patients, after undergoing neo-adjuvant chemotherapy show excellent pathologic complete response rates. However, patients who harbour residual disease even after the neo-adjuvant chemotherapy, exhibit abysmal prognosis. The relapse of TNBC is combined with greater risks of metastasis to the lungs or the central nervous system. However, a lower risk metastasis to the bones and survival rates of nearly one year alone is also observed.

Hence, to summarize, TNBC has 2 major setbacks, namely: poor prognosis and lack of recognized targets or predictors for therapeutic response. Hence, the need of the hour calls for diagnostically discriminating specific markers that can be aimed for treatment by tailored therapies and used to foresee the responses to chemotherapy.

Characteristics of TNBC

- TNBC is argumentative in nature than the other forms of BC owing to the reason that there are scarcer targeted medicines to treat TNBC. They frequently metastasize and relapse post treatment.
- TNBC is advanced than other forms of BC and on a scale of 1 to 3, TNBC is often grade 3.
- TNBC cells mimics the basal cells which lines the breast ducts and hence the name "basal-like" which are more violent, higher order cancers. However not all basal-like BC's are triple negative and not all TNBC's are basal-like.

Although anyone is susceptible to TNBC, it is more commonly found in 3 sects of people:

- Younger people: Women under 50 years are incrementally prone to be diagnosed with TNBC whereas all the other types of BC's are more easily diagnosed in women of any age group.
- African-American and Hispanic women: Women of African-American and Hispanic origin are more susceptible to TNBC than Asian and non-Hispanic white women.
- People with a *BRCA1* mutation: TNBC is found in nearly 70% of breast cancers patients who expressed inherited *BRCA* mutation, especially mutations in the *BRCA1* gene.

A review published in the British Journal of Cancer-2018 states that there is a low probability of recurrence of breast cancer if the patient has remained disease free for a period of 5 years post treatment. However, it has also been reported that the predominant risk of relapse commonly emerges in the first few years after treatment and post 5 years, the threat of re-emergence is greatly minimized.

A recent publication in the Journal of Clinical Oncology states that TNBC patients are more liable to develop metastasis in the brain and lungs but however the survival rates are greater if metastasis progresses to the bones.

TREATMENT OPTIONS FOR TNBC

In general, BCs are diagnosed at later stages which results in poor prognosis and based on the cancer sub-type and stage the treatment regimens are performed which includes surgery, radiation and/or chemotherapy. The survival rates of BC patients have increased greatly through mastectomy and chemotherapy. The post-treatment

psychological impact on patients have also minimized through more refined surgical procedures. Advanced modern-day treatments like immunotherapy, hormone therapy and other types of biologic therapy & stem cell transplantation is also being implemented currently. However, the generalized treatment for BC involves cytotoxic and immunotherapeutic agents of which the only acknowledged treatment regimen for the TNBC sub-type is cytotoxic chemotherapy. Combination treatment of surgery, radiation and chemotherapy are practiced these days to treat TNBC. However, in order to achieve Pathologic Complete Response (pCR) and better overall & disease-free longevity rates, neoadjuvant chemotherapy i.e., chemotherapeutic treatment ahead of surgery is being practiced.

Surgery

Lumpectomy: A procedure that necessitates the removal of the tumour or lump from the breast and ensuring that the nearby lymph nodes are free of cancer and absence of metastasis.

Mastectomy: A procedure involving the complete removal of the breast(s) and ensuring that the nearby lymph nodes are free of cancer and absence of metastasis.

Radiation

Radiation therapy involves the use of high-energy radiations on the tumor regions and breasts post lumpectomy to ensure termination of any residual cancer cells.

Chemotherapy

Chemotherapy is generally addressed to terminate cancer cells in cases of metastasis where they traverse to different parts of the body from the primary site and to eventually ensure the minimalistic chances of recurrences.

PARP Inhibitors

The main task of PARP enzyme (Poly ADP-Ribose Polymerase) is to repair DNA damage in both cancer and healthy cells. Several studies prove that drugs hindering the action of PARP minimize the survival of cancer cells, especially those with *BRCA1* or *BRCA2* mutation as they prevent DNA repair mechanisms. Some of the most commonly used PARP inhibitors administered to advanced-stage HER2-negative BC patients with mutations in *BRCA1* or *BRCA2* are lynparza (chemical name: olaparib) and talzenna (chemical name: talazoparib).

Immunotherapy

Immunotherapeutic drugs enhance the immune system and enable them to target cancer cells. One such drug is tecentriq (chemical name: atezolizumab), an immune checkpoint inhibitor that specifically aims at the PD-L1 protein which aids cancer cells in evading the immune system and thereby facilitating the death of cancer cells. Tecentriqin, in combination with Abraxane (chemical name: albumin-bound paclitaxel or nab-paclitaxel) was developed as the first regimen for unrespectable locally advanced or metastatic triple-negative PD-L1-positive BC.

SIDE-EFFECTS OF CANCER TREATMENTS

Hair Loss

The first after-effect of cancer treatment especially chemotherapy is hair loss which can be experienced within two to four weeks of starting chemotherapy.

Nausea

Most patients experience sickness and tiredness for a day or two after each chemotherapy session.

Skin Changes

Another major after-effect of cancer treatment, especially radiation therapy is reddening or skin peeling in and around the region of radiation.

Risks of Breast Cancer

There are umpteen environmental traits leading to the progression of BC like age, high hormonal levels, use of tobacco, obesity etc. However, genetic factor also has a crucial part in the advancement of BC and nearly 5–10% of the BC cases may be affiliated with aberrations in *BRCA1* and *BRCA2* genes. The *BRCA1*/2 genes are autosomal dominant and tumour suppressor genes which are located on chromosomes 17 and 13 accordingly and are found to be mutated in nearly 30–40% of BCs. It has been proven that a woman's probability of developing BC roughly doubles if there's a first-degree relative (mother, sister, or daughter) who's been confirmed with BC within the family. Age is yet another inevitable liability for BC because most cases reported are in women below 50 years of age.

A series of inter-connected factors like environment, genetics, hormones, socio-biology and physiology are associated with BC development and progression. Among them, some factors are inevitable while the others are lifestyle-related. Few of the identified risk factors for BC and its sub-types include:

- **Origin:** African-American or Hispanic
- **Age:** Under 50 years of age
- **Genetic:** *BRCA1/2* mutations
- Not breastfeeding
- Obesity
- Breast density
- Exposure: ionizing radiation and gadgets, carcinogens
- Nutritional factors: excess intake of caffeine, alcohol, fats, tobacco and red meat.
- Hormonal history: women with more number of menstrual cycles during her lifetime has greater risks of developing BC.
- Oral contraceptives and hormone replacement therapy
- Weak immune system

NATURAL AGENTS

Natural agents derived from different class was tested for their anticancer property. Active agents such as flavonoids, alkaloids, terpenoids have already shown promising activities against BC (Hasanpourghadi *et al*., 2018). In this chapter we have listed various natural agents that were tested (Table 1) against TNBC and their mechanisms of action have also been postulated.

Schisandrin A on TNBC

Schisandrin A (SchA) is a lignin and one of the major bioactive phytochemicals that is found in the plant species *Schisandra chinensis* (Turcz.) Baill. (Schisadraceae). Xu *et al*., (2019) reported that SchA inhibits TNBC cells such as BT549 and MDA-MB-231 which was determined through *in vitro* studies and also through MDA-MB-231 induced mouse xenograft model. Administration of SchA inhibits TNBC cell propagation by cell cycle arrest and apoptosis induction. Moreover, it is observed that Wnt signalling was abundant in TNBC cells, but supplementation of SchA significantly suppressed the Wnt signalling pathway. Also, treatment of SchA activated C/EBP Homologous Protein (CHOP), stress mediators in endoplasmic reticulum such as p-elF2α and Activating Transcription Factor (ATF) 4 expressions

Table 1. The list of natural agents and its mechanism of actions against TNBC cells in vitro and in vivo.

Natural agent	Cancer type	Mechanism of action	
Schisandrin A (SchA)	MDA-MB-231 and BT-549	Sch A Induces apoptosis Sch A suppress tumor in MDA-MB-231 induced xenograft mice	Xu *et al.,* (2019)
Hibiscus flower extract	MCF-7 and MDA-MB-231 cells	Hibiscus flower extract induce apoptosis dose-dependently	Nguyen *et al.,* (2019)
Artemisia annua L. extract (AALE)	MDA-MB-231 cells MDA-MB-231 cells induced xenograft mice	AALE inhibits the cell viability of MDA-MB-231 cells AALE induces cell cycle arrest at S and G2/M phase AALE induces apoptosis by inducing the activation of caspase 3. AALE decreased the tumor growth in vivo AALE induces apoptosis *in vivo.*	Rassias & Weathers, (2019)
Ethanolic extract of *Cyperus rotundus* L. (EECR)	MDA-MB-231 and MDA-MB-468 cells	EECR inhibits cell proliferation of MDA-MB-231 and MDA-MB-468 cells. EECR induces apoptosis by modulating the expressions of Bcl-2 and Bax.	Kai *et al.,* (2019)
Withania somnifera Protein fraction	MDA-MB-231 cells	WSPF induces ROS-mediated mitochondrial mediated apoptosis WSPF modulates the Bcl-2/bax ratio, G_2/M phase cell cycle arrest	Dar *et al.,* (2019)
(-)-Oleocanthal (OC)	BT474 inoculated orthotopic mice	OC reduced the recurrent tumor when compared to control animals OC treatment resulted that upregulation of E-Cadherin and downregulation of vimentin.	Siddique *et al.,* (2019)
Essential oil of *Cyphostemma juttae* (EOCJ)	MDA-MB-231 and SUM 149 cells	Inhibit the proliferation of MDA-MB-231 and SUM 149 cells. EOCJ inhibit the activation of NF-κB. EOCJ inhibit the apoptotic genes of XIAP, Bcl-2 and Survivin.	Zito *et al.,* (2019)
Nor-Wogonin	MDA-MB-231, BT-549, HCC70, and HCC1806 TNBC cells	It inhibits the viability of MDA-MB-231, BT-549, HCC70, and HCC1806 TNBC cells. It reduced the expressions of cell cycle proteins such as cyclin D1, cyclin B1, and CDK1. Nor-wogonin induces mitochondrial apoptosis, decreased in the mitochondrial membrane potential ($\Delta\Psi m$), increased in Bax/Bcl-2 ratio, and activation of caspase-3. It attenuated the NF-κB expression and also activation of STAT3 pathways.	Abd El-Hafeez *et al.,* (2019)
Baicalein	MDA-MB-231/IR cells	Baicalein inhibits the viability of MDA-MB-231/IR cells Baicalein inhibits the NF-κB activation Baicalein suppressed the stem cell-like characteristics, such as formation of mammosphere, side population, expression of Oct3/4 and ABCG2, and CD44highCD24low population in MDA-MB-231/IR TNBC cells	Koh *et al.,* (2019)
Tertrandrine	MDA-MB-231 cells	Tetrandrine inhibits the viability of MDA-MB-231 TNBC cells. It also induces apoptosis by dose-dependently that was confirmed by the Annexin V/PI staining. Tetrandrine induced autophagy by diminishing the expression of p62/SQSTM1, enhancing the Beclin1 and LC3-II/LC3-I expressions, suppressing the PI3K/AKT/mTOR up-regulating the expression of PTEN.	Guo *et al.,* (2019)

in TNBC cells. SchA potentially induces apoptosis in TNBC cells by modulating the key apoptotic mediators. Finally, the authors were able to prove SchA's inhibitory effects in the *in vivo* xenograft mouse model induced with MDA-MB-231 cells.

Hibiscus Rosa-Sinensis Linn. (Malvaceae)

The extract of *H. rosa-sinesis* is well known for its medicinal and anticancer traits as it harbours antioxidant, antimicrobial, anti-adipogenic and hypolipidemic effects (Lingesh *et al*., 2019). However, the role of *H. rosa-sinesis* on BC has not yet been fully studied. Nguyen *et al*., (2019) revealed that Hibiscus extract selectively induced dose-dependent apoptosis in TNBC cells. Notably, treatments involving hibiscus extract showed enhanced apoptosis when administered along with chemotherapeutic drugs (taxol and cisplatin) in TNBC cells than when treated alone. In addition, the combined effects of hibiscus extract and chemotherapeutic drugs enhanced oxidative stress and minimized mitochondrial membrane potential better than hibiscus extract administered alone.

Sophoraflavanone G on TNBC

Sophoraflavanone G (SG) is an active compound isolated from *Sophora flavescens* Aiton (Fabaceae) with both anti-inflammatory and anti-tumour properties. MDA-MB-231 cells were exercised with different concentrations of SG and the cell survival rates were estimated through MTT assay. It is concluded that SG produces reactive oxygen species, nuclear condensation, DNA fragmentation and also accelerated cell death in MDA-MB-231 cells upon treatment. SG also inhibited the MAPK pathway which eventually causes suppression of migration and invasion. Along with induced apoptosis, enhanced levels of cleaved caspase-3, caspase-8 and caspase-9 were observed upon SG administration. SG application also enabled increased bax expressions and decreased Bcl-2, Bcl-xL expressions along with excess cytochrome c release from mitochondria into the cytoplasam (Huang *et al*., 2019).

Berberine on TNBC

Berberine (BBR) is a well-known alkaloid used against various cancer cell lines which effectively induces apoptosis by inhibiting cell propagation. TNBC cell lines such as MDA-MB-231, MDA-MB-453, and BT-549 were tested using BBR. BBR effectively suppressed cell proliferation in MDA-MB-231 (0, 6.25, 12.5, and 25 μM) and MDA-MB-468 (0, 3, 6, and 12 μM) dose-dependently. BBR administration enhances arrest in cell cycle in the S+G2/M phase in MDA-MB-453 and MDA-MB-231 cells, while a surge in G0/G1 phase was noted in BBR-treated BT-549

and MDA-MB-468 lines. Administration of BBR decreased the levels of cyclin dependent kinase 1 and cyclin A expressions in MDA-MB-453 and MDA-MB-231 cells which was verified by western blot. Alternatively, in BBR-treated BT-549 and MDA-MB-468 cells, decreased western blot expressions of cyclin dependent kinase 4 (cdk4) and Cyclin D were observed (Lin *et al*., 2019). Hence, the study concludes that BBR can potentially induce apoptosis by modulating the cell cycle check points.

Naringenin

Naringenin is a well-known flavonoid, reported to possess innumerable applications in the pharmaceutical industry owing to its antioxidant and antiinflammatory properties. Zhao *et al*., (2019) researched the antitumor activity of naringenin in MDA-MB-231 TNBC cells and 7, 12-dimethylbenz[a] anthracene (DMBA)-triggered BC animal model in rats to understand its mechanism of action and concluded that, administration of Naringenin inhibits cell progression both dose and time dependently. This after-effect was accompanied by cell cycle halt in G0/G1 phase accompanied by cell deposition in sub-G1 phase (75%) and apoptosis. In DMBA-induced animal model, naringenin treatment minimized the incidence of tumour (45.55, 40, and 27.67%) and reduced tumour burden (78.7, 35.4, and 1.2 g) dose-dependently. In conclusion, alterations in antioxidant and biochemical attributes linked to inflammation that pose as necessary features for anticancer activity were seen upon administration of Naringenin.

Shikonin

Shikonin is a naphthoquinone pigment and it is frequently derived from the plant *Lithospermum erythrorhizon* Siebold & Zucc. (Boraginaceae) found in China. The molecular weight of the shikonin is 288KDa. For many years *L. erythrorhizon* have been used in Chinese medicine for treating various diseases including measles, carbuncles burn and macular eruptions (Chen *et al*., 2017). Shikonin is also used for the treatment of Hypertrophic Scar Model (Deng *et al*., 2018). Shikonin is extensively studied by researchers for its anticancer property against diverse cancer types (Wang *et al*., 2018). However, shikonin protects the H9C2 cardiomyocytes from the injury caused by hypoxia/reoxygenation by stimulating the PI3K/Akt pathway (Wang *et al*., 2018). Recently, Chen *et al*., (2019) revealed that shikonin diminishes the viabilities of 4T1 and MDA-MB-231 (TNBC) cell lines. Surprisingly, shikonin administration displays reduced cytotoxicity against normal mammary epithelial cell line - MCF-12A. In addition, it causes reversing of Epithelial-To-Mesenchymal Transition (EMT) in 4T1 and MDA-MB-231 cell lines. Also, other findings reveal that Shikonin can effectively suppress the infiltration and migration of tumour cells,

up-regulate the levels of E-cadherin expression, down-regulate vimentin, Snail & N-cadherin expressions and reorganize vimentin & F-actin (cytoskeletal proteins). Shikonin inhibits β-catenin signalling by hindering β-catenin expression, nuclear accumulation of β-catenin's binding to T cell factor consensus oligos and specific EMT-related genes transcription which results the inhibition of EMT transformation. Furthermore, shikonin up-regulates the expression of Glycogen Synthase Kinase 3β (GSK-3β) that eventually enhances the β-catenin phosphorylation thereby decreasing the expressions of β-catenin. In addition, supplementation of shikonin inhibits lung metastasis significantly in MDA-MB-231 inoculated NOD/SCID mice with very little toxicity. Similarly, the *in vitro* histological studies reveal that shikonin can elevate the levels of phosphorylated β-catenin, GSK-3β & E-cadherin and can decrease the expressions of β-catenin & vimentin in pulmonary metastatic foci. Hence researchers conclude that shiknoin can effectively suppress TNBC metastasis via blocking the β-catenin signalling pathway and that it acts as a key candidate in treating TNBC.

Artemisia Annua Linn. (Asteraceae)

A. annua is a traditionally utilized herb in Chinese medicine. Generally, it is used to treat ailments like Malaria and certain autoimmune diseases (Wu *et al*., 2016; Ruan *et al*., 2019). A water-soluble polysaccharide isolated from *A. annua* inhibits the proliferation of HepG2 cell line (Yan *et al*., 2019). Rassias & Weathers, (2019) report that the dried leaf of *A. annua* effectively inhibit the progression of A549 non-small lung cancer cells. Similarly, Lang and his colleagues used *A. annua* leaves extract (AALE) on MDA-MB-231 (TNBC) cells and reported that it can effectively inhibit the viability of MDA-MB-231 cells. They also stated that among the abundant ingredients of AALE's arteannuin B, casticin and chrysosplenol D suppressed the survival ability in MDA-MB-231 TNBC cell line, however 6,7-dimethoxycoumarin and arteannuic acid did not possess this trait. Studies also prove that the administration of AALE leads to the augmentation of cells at S and G2/M phase accompanied by a very low mitochondrial membrane potential. Further, it is shown that AALE induces apoptosis by activating the caspase 3 expression. In order to justify the findings, when AALE is administered to MDA-MB-231-induce xenograft mice, researchers prove that it possess the potential to inhibit tumour growth and induce apoptosis (Lang *et al*., 2019).

Cyperus Rotundus Linn. (Cyperaceae)

C. rotundus is among the predominant traditionally exploited plants in Chinese medicine and is used to treat various diseases. Isolated sesquiterpenes from *C. rotundus* acts as a modulator of estrogen receptor (Parker *et al*., 2009). It is reported

for harbouring various pharmacological benefits including anti-inflammatory, anti-bacterial and antioxidant attributes (Kamala *et al*., 2018; Cheypratub *et al*., 2018). The application of the ethanolic extract of *C. rotundus* (EECR) on MDA-MB-468 and MDA-MB-231 cells shows that they hinder cell progression dose-dependently. They also possess the ability to trigger G0/G1 phase arrest in cell cycle and provoke apoptosis by altering Bax and Bcl-2 expressions in western blot. Kai and his colleagues treated TNBC cells with 5mM of 3-MA and reported that it effectively inhibits autophagy which subsequently increases the sensitivity to EECR (Kai *et al*., 2019).

Withania Somnifera Linn. (Dunal) (Solanaceae)

W. somnifera, is a habitually used Indian Ayurvedic herb which also goes by the name 'Indian Ginseng' for its versatile medicinal properties (Dar *et al*., 2016). In recent times, it is reported that *W. somnifera* ameliorates oxidative stress and BPA-induced cognitive dysfunction in Male Swiss albino mice (Birla *et al*., 2019). Kumar *et al.,* (2019) reveal that *W. somnifera* show protection against trace metal oxide (zinc oxide nanoparticles)-induced toxicity in mouse model. Withaferin-A (WA) is a key ingredient of *WS* that suppresses the ovalbumin induced airway inflammation (Zhao *et al*., 2019). Another study depicts that MDA-MB-231 (TNBC) cells upon treatment with *W. somnifera* Protein fraction (WSPF) induces Reactive Oxygen Species (ROS) which destructs mitochondria leading to the activation of cell death in them. It also results in the dys-regulation of Mitochondrial Membrane Potential (MMP), alters the Bax/Bcl-2 ratio and activates caspase-3. Also, arrest in G2/M-phase, nuclear morphological changes and nuclear lamin A/C proteins cleavage are observed (Dar *et al*., 2019).

(-)-Oleocanthal

(-)-Oleocanthal (OC) is a compound possessing phenolic nature that is extensively available naturally in Extra-Virgin Olive Oil (EVOO). It exerts anti-inflammatory and anticancer potentials which have been reported against various cell lines and animal models (Elnagar *et al*., 2011; Scotece *et al*., 2013). Administration of OC at the dose of 10mg/kg to BT474 inoculated orthotopic mice did not affect the tumour recurrence but it significantly reduced the recurrent tumour when compared to the control animals. Supplementation of OC to BT-474 inoculated orthotopic mice leads to the stimulation of E-cadherin (epithelial marker) expression and hinders vimentin (mesenchymal marker) expression in recurrent tumours when compared to control tumour bearing animals. Also, it is proved that OC reduces the activation of HER2 and MET receptors, which is displayed through minimized phosphorylation levels of these proteins (Siddique *et al*., 2019).

Cyphostemma Juttae (Planch.) Alston (Vitaceae)

For the treatment of snake bites as a traditional medicine the roots of *C. junceum* is used (Teklehaymanot & Giday, 2007). Zito *et al*., (2019) researched and proved that the essential oil of *C. juttae* contains 39 compounds such as phytol, carvacral, linalool, limonene, piperitenon, etc. Also, they evaluated the cytotoxic potential of the essential oil of *C. juttae* on SUM 149 and MDA-MB-231 (TNBC) cells and observed that it effectively inhibits the TNBC cells. EOCJ also inhibits the triggering of NF-κB in SUM 149 & MDA-MB-231 (TNBC) cells, down-regulates the key apoptotic genes such as *XIAP*, survivin & *Bcl2* thus proving the fact that by hindering the up-regulation of NF-κB, that essential oil of *C. juttae* sensitizes the TNBC cells.

Nor-Wogonin

Scutellaria baicalensis Georgi (Lamiaceae) produces two key active ingredients namely wogonin and nor-wogonin. Nor-wogonin is chemically named as 5,7,8-trihydroxyflavone but is however structurally related to wogonin with a minor difference. Both the compounds structurally differ from one another by the existence of 'OMe' group in nor-wogonin at the C-8 position rather than the 'OH' group which is present only in nor-wogonin (Hui *et al*., 2002; Miyasaki *et al*., 2013). Nor-wogonin harbours certain biological traits like antiviral, anti-inflammatory, anticancer and antidiabetic properties (Inoue-Choi *et al*., 2016; Ahmed *et al*., 2018). Former reports state the effective elimination of HL-60 leukaemia cells by nor-wogonin by apoptosis when compared to wogonin (Chow *et al*., 2008).

Abd El-Hafeez *et al*., (2019) reports that upon the administration of nor-wogonin, significant inhibition in the cell progression and decrease in cell viability of HCC70, BT-549, HCC1806 and MDA-MB-231 (TNBC) cells was observed and contrastingly it shows no/minimal effects on AG11132 and MCF-10A (non-tumorigenic) cells. Also, nor-wogonin affected TNBC cells *via* reducing cell cycle proteins expressions like CDK1, cyclin B1 and cyclin D1. In addition, nor-wogonin induces mitochondrial apoptosis, decreases the Mitochondrial Membrane Potential (MMP), enhances the Bax/Bcl-2 ratio and activates caspase-3. Further, it attenuates the NF-κB expression and also activates STAT3 pathways.

Baicalein

Scutellaria baicalensis Georgi is among the many traditionally used medicinal herbs and the roots of this herb produces an active compound named Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one) (Kim *et al*., 2008). Baicalein is reported to possess many health benefits including hepatoprotective, antibacterial,

antiviral, antidiabetic, anti-inflammatory and anticancer activities (Zhou *et al*., 2018; Yan *et al*., 2018; Yin *et al*., 2018; Pu *et al*., 2019; Zhao *et al*., 2019; Qinghe *et al*., 2019). Resistance developed against chemotherapy and radiation-therapy is still considered a common hurdle in TNBC therapeutics. However, Koh *et al*., (2019) irradiated the parental MDA-MB-231 cells with 2Gy irradiation (25 times) and developed the resistant TNBC MDA-MB-231/IR cells. Further, they also evaluated the inhibitory mechanism involved behind Baicalein against these MDA-MB-231/IR TNBC cells. Molecular pathways namely TNF signalling pathway, Toll-Like Receptor (TLR) pathway and NF-κB pathway were up-regulated in the MDA-MB-231/IR cells when it was analysed by Database for Annotation, Visualization and Integrated Discovery. Further, it is noted that Baicalein sensitizes radio- and chemo-resistant TNBC/IR cells and enhances the apoptosis mechanism, however, on the other hand it suppresses the stem cell-like characteristics like formation of mammosphere, $CD44^{high}CD24^{low}$ population and expressions of Oct3/4 & ABCG2 in MDA-MB-231/IR TNBC cells.

Tetrandrine

The roots of the plant *Stephania tetrandra* S. Moore (Menispermaceae) produces a bisbenzylisoquinoline alkaloid by the name tetrandrine (Liu *et al*., 2016). Tetrandrine is used as an anticancer agent for many types of cancers including colorectal, Cervical, glioblastoma and lung cancer (Li *et al*., 2019; Zhang *et al*., 2018). Guo & Pei, (2019) reveals that tetrandrine inhibits MDA-MB-231 (TNBC) cell's viability. Moreover, it also induces apoptosis dose-dependently which is confirmed via Annexin-V/PI staining. Further, it is observed that Tetrandrine induces autophagy by diminishing the expression of p62/SQSTM1, enhancing the LC3-II/LC3-I & Beclin1 expressions, suppressing the PI3K/AKT /mTOR and by up-regulating the expression of PTEN.

CONCLUSION

TNBC is the aggressive form of BC and the choice of treatments are greatly deficient owing to the dearth of its receptors. However, the above-mentioned natural components showed promising activities against TNBC. Natural agents such as Hibiscus extract, Schisandrin A (SchA), (-)-Oleocanthal (OC), (-)-Oleocanthal (OC), Baicalein, Tertrandrine, *Artemisia annua* extract (AALE), etc., were able to hinder cell viability and provoke apoptosis in both *in vitro* and *in vivo* models of TNBC and further clinical trials are warranted to use these agents against TNBC patients.

REFERENCES

Abd El-Hafeez, A. A., Khalifa, H. O., Mahdy, E. A. M., Sharma, V., Hosoi, T., Ghosh, P., ... Kawamoto, S. (2019). Anticancer effect of nor-wogonin (5, 7, 8-trihydroxyflavone) on human triple-negative breast cancer cells via down regulation of TAK1, NF-κB, and STAT3. *Pharmacological Reports*, *71*(2), 289–298. doi:10.1016/j.pharep.2019.01.001 PMID:30826569

Ahmed, Q. U., Sarian, M. N., Mat So'ad, S. Z., Latip, J., Arief Ichwan, S., Hussein, N., ... Fakurazi, S. (2018, November 15). Methylation and Acetylation Enhanced the Antidiabetic Activity of Some Selected Flavonoids: *In vitro*, Molecular Modelling and Structure Activity Relationship-Based Study. *Biomolecules*, *8*(4), 149. doi:10.3390/biom8040149

Angahar, L. T. (2017). An overview of breast cancer epidemiology, risk factors, pathophysiology, and cancer risks reduction. *MOJ Biol Med*, *1*(4), 92–96. doi:10.15406/mojbm.2017.01.00019

Birla, H., Keswani, C., Rai, S. N., Singh, S. S., Zahra, W., Dilnashin, H., ... Singh, S. P. (2019). Neuroprotective effects of *Withania somnifera* in BPA induced-cognitive dysfunction and oxidative stress in mice. *Behavioral and Brain Functions*, *15*(1), 9. doi:10.118612993-019-0160-4 PMID:31064381

Chen, C., Xiao, W., Huang, L., Yu, G., Ni, J., Yang, L., ... Hu, G. (2017). Shikonin induces apoptosis and necroptosis in pancreatic cancer via regulating the expression of RIP1/RIP3 and synergizes the activity of gemcitabine. *American Journal of Translational Research*, *9*(12), 5507–5517. PMID:29312502

Chen, Y., Chen, Z. Y., Chen, L., Zhang, J. Y., Fu, L. Y., Tao, L., ... Shen, X. C. (2019). Shikonin inhibits triple-negative breast cancer-cell metastasis by reversing the epithelial-to-mesenchymal transition via glycogen synthase kinase 3β-regulated suppression of β-catenin signalling. *Biochemical Pharmacology*, *166*, 33–45. doi:10.1016/j.bcp.2019.05.001 PMID:31071331

Cheypratub, P., Leeanansaksiri, W., & Eumkeb, G. (2018). The synergy and mode of action of *Cyperus rotundus* L. extract plus ampicillin against ampicillin-resistant *Staphylococcus aureus*. *Evidence-Based Complementary and Alternative Medicine*, *2018*, 1–11. doi:10.1155/2018/3438453 PMID:29849704

Chow, J. M., Huang, G. C., Shen, S. C., Wu, C. Y., Lin, C. W., & Chen, Y. C. (2008). Differential apoptotic effect of wogonin and nor-wogonin via stimulation of ROS production in human leukemia cells. *Journal of Cellular Biochemistry*, *103*(5), 1394–1404. doi:10.1002/jcb.21528 PMID:17955493

Cox, R. F., & Morgan, M. P. (2013). Microcalcifications in breast cancer: Lessons from physiological mineralization. *Bone*, *53*(2), 437–450. doi:10.1016/j.bone.2013.01.013 PMID:23334083

Dar, P. A., Mir, S. A., Bhat, J. A., Hamid, A., Singh, L. R., Malik, F., & Dar, T. A. (2019). An anti-cancerous protein fraction from *Withania somnifera* induces ROS-dependent mitochondria-mediated apoptosis in human MDA-MB-231 breast cancer cells. *International Journal of Biological Macromolecules*, *135*, 77–87. doi:10.1016/j.ijbiomac.2019.05.120 PMID:31121227

Dar, P. A., Singh, L. R., Kamal, M. A., & Dar, T. A. (2016). Unique Medicinal Properties of *Withania somnifera*: Phytochemical Constituents and Protein Component. *Current Pharmaceutical Design*, *22*(5), 535–540. doi:10.2174/1381612826666151125001751 PMID:26601969

Deng, X., Chen, Q., Qiang, L., Chi, M., Xie, N., Wu, Y., ... Xie, Y. (2018). Development of a porcine full-thickness burn hypertrophic scar model and investigation of the effects of shikonin on hypertrophic scar remediation. *Frontiers in Pharmacology*, *9*, 590. doi:10.3389/fphar.2018.00590 PMID:29922164

Elnagar, A. Y., Sylvester, P. W., & El Sayed, K. A. (2011). (−)-Oleocanthal as a c-Met inhibitor for the control of metastatic breast and prostate cancers. *Planta Medica*, *77*(10), 1013–1019. doi:10.1055-0030-1270724 PMID:21328179

Guo, Y., & Pei, X. (2019). Tetrandrine-induced autophagy in MDA-MB-231 triple-negative breast cancer cell through the inhibition of PI3K/AKT/mTOR signalling. *Evidence-Based Complementary and Alternative Medicine*, *2019*, 1–11. doi:10.1155/2019/7517431 PMID:30713576

Hariharan, N., & Rao, T. S. (2019). The evolving role of pathologic complete response in breast cancer. *South Asian Journal of Cancer*, *8*(4), 210. doi:10.4103ajc.sajc_67_19 PMID:31807476

Hasanpourghadi, M., Pandurangan, A. K., & Mustafa, M. R. (2018). Modulation of oncogenic transcription factors by bioactive natural products in breast cancer. *Pharmacological Research*, *128*, 376–388. doi:10.1016/j.phrs.2017.09.009 PMID:28923544

Huang, G. C., Chow, J. M., Shen, S. C., Yang, L. Y., Lin, C. W., & Chen, Y. C. (2007). Wogonin but not Nor-wogonin inhibits lipopolysaccharide and lipoteichoic acid-induced iNOS gene expression and NO production in macrophages. *International Immunopharmacology*, *7*(8), 1054–1063. doi:10.1016/j.intimp.2007.04.001 PMID:17570322

Huang, W. C., Gu, P. Y., Fang, L. W., Huang, Y. L., Lin, C. F., & Liou, C. J. (2019). Sophoraflavanone G from *Sophora flavescens* induces apoptosis in triple-negative breast cancer cells. *Phytomedicine*, *61*, 152852. doi:10.1016/j.phymed.2019.152852 PMID:31035052

Hui, K. M., Huen, M. S., Wang, H. Y., Zheng, H., Sigel, E., Baur, R., ... Xue, H. (2002). Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from *Scutellaria baicalensis* Georgi. *Biochemical Pharmacology*, *64*(9), 1415–1424. doi:10.1016/S0006-2952(02)01347-3 PMID:12392823

Inoue-Choi, M., Sinha, R., Gierach, G. L., & Ward, M. H. (2016). Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP diet and health study. *International Journal of Cancer*, *138*(7), 1609–1618. doi:10.1002/ijc.29901 PMID:26505173

Kamala, A., Middha, S. K., Gopinath, C., Sindhura, H. S., & Karigar, C. S. (2018). *In vitro* antioxidant potentials of *Cyperus rotundus* L. rhizome extracts and their phytochemical analysis. *Pharmacognosy Magazine*, *14*(54), 261–267. doi:10.4103/pm.pm_228_17 PMID:29720842

Khazaee-Pool, M., Pashaei, T., Jahangiry, L., Ponnet, K., & Gholami, A. (2017). Exploring breast cancer preventive lifestyle and social support of Iranian women: A study protocol for a mixed-methods approach. *International Journal for Equity in Health*, *16*(1), 97. doi:10.118612939-017-0592-0 PMID:28592298

Kim, B. W., Lee, E. R., Min, H. M., Jeong, H. S., Ahn, J. Y., Kim, J. H., ... Cho, S. G. (2008). Sustained ERK activation is involved in the kaempferol-induced apoptosis of breast cancer cells and is more evident under 3-D culture condition. *Cancer Biology & Therapy*, *7*(7), 1080–1089. doi:10.4161/cbt.7.7.6164 PMID:18443432

Koh, S. Y., Moon, J. Y., Unno, T., & Cho, S. K. (2019). Baicalein suppresses stem cell-like characteristics in radio and chemoresistant MDA-MB-231 human breast cancer cells through up-regulation of IFIT2. *Nutrients*, *11*(3), 624. doi:10.3390/nu11030624 PMID:30875792

Kumar, J., Mitra, M. D., Hussain, A., & Kaul, G. (2019). Exploration of immunomodulatory and protective effect of *Withania somnifera* on trace metal oxide (zinc oxide nanoparticles) induced toxicity in Balb/c mice. *Molecular Biology Reports*, *46*(2), 2447–2459. doi:10.100711033-019-04705-x PMID:30847852

Lang, S. J., Schmiech, M., Hafner, S., Paetz, C., Steinborn, C., Huber, R., ... Simmet, T. (2019). Antitumor activity of an *Artemisia annua* herbal preparation and identification of active ingredients. *Phytomedicine*, *62*, 152962. doi:10.1016/j.phymed.2019.152962 PMID:31132755

Lee, H.-B., & Han, W. (2014). Unique Features of Young Age Breast Cancer and Its Management. *Journal of Breast Cancer*, *17*(4), 301–307. doi:10.4048/jbc.2014.17.4.301 PMID:25548576

Li, J., Wang, Q., Wang, Z., Cui, N., Yang, B., Niu, W., & Kuang, H. (2019). Tetrandrine inhibits colon carcinoma HT-29 cells growth via the Bcl-2/Caspase 3/PARP pathway and G1/S phase. *Bioscience Reports*, *39*(5), BSR20182109. doi:10.1042/BSR20182109 PMID:31040202

Lin, Y. S., Chiu, Y. C., Tsai, Y. H., Tsai, Y. F., Wang, J. Y., Tseng, L. M., & Chiu, J. H. (2019). Different mechanisms involved in the berberine-induced antiproliferation effects in triple-negative breast cancer cell lines. *Journal of Cellular Biochemistry*, *120*(8), 13531–13544. doi:10.1002/jcb.28628 PMID:30957305

Lingesh, A., Paul, D., Naidu, V. G. M., & Satheeshkumar, N. (2019). AMPK activating and anti adipogenic potential of *Hibiscus rosa sinensis* flower in 3T3-L1 cells. *Journal of Ethnopharmacology*, *233*, 123–130. doi:10.1016/j.jep.2018.12.039 PMID:30593890

Liu, T., Liu, X., & Li, W. (2016). Tetrandrine, a Chinese plant-derived alkaloid, is a potential candidate for cancer chemotherapy. *Oncotarget*, *7*(26), 40800. doi:10.18632/oncotarget.8315 PMID:27027348

Ly, M., Antoine, M., André, F., Callard, P., Bernaudin, J. F., & Diallo, D. A. (2011). Breast cancer in Sub-Saharan African women [review]. *Bulletin du Cancer*, *98*(7), 797–806. doi:10.1684/bdc.2011.1392 PMID:21700549

Miyasaki, Y., Rabenstein, J. D., Rhea, J., Crouch, M. L., Mocek, U. M., Kittell, P. E., ... Liu, G. Y. (2013). Isolation and characterization of antimicrobial compounds in plant extracts against multidrug-resistant *Acinetobacter baumannii. PLoS One*, *8*(4), e61594. doi:10.1371/journal.pone.0061594 PMID:23630600

Nguyen, C., Baskaran, K., Pupulin, A., Ruvinov, I., Zaitoon, O., Grewal, S., ... Pandey, S. (2019). Hibiscus flower extract selectively induces apoptosis in breast cancer cells and positively interacts with common chemotherapeutics. *BMC Complementary and Alternative Medicine*, *19*(1), 98. doi:10.118612906-019-2505-9 PMID:31060537

Pandurangan, A. K., Kanagesan, S., Narayanaswamy, R., Esa, N. M., & Padmanabhan, P. (2015). *Applications of NanoBioMaterials: Nanobiomaterials in Cancer Therapy.* In A. M. Grumezescu (Ed.), *NanoBioMaterials based delivery of drugs in various cancer therapies: Classifying the mechanisms of action (using Biochemical and Molecular biomarkers)* (Vol. 7, pp. 331–365). Elsevier Publisher.

Pandurangan, A. K., & Mustafa, M. R. (2018). Anticancer Plants: Natural Products and Biotechnological Implements. In The therapeutic strategies of natural agents on Triple-negative breast cancer. Springer International Publishing.

Parker, J. S., Mullins, M., Cheang, M. C. U., Leung, S., Voduc, D., Vickery, T., ... Bernard, P. S. (2009). Supervised risk predictor of breast cancer based on intrinsic subtypes. *Journal of Clinical Oncology*, *27*(8), 1160–1167. doi:10.1200/JCO.2008.18.1370 PMID:19204204

Pu, W. L., Bai, R. Y., Zhou, K., Peng, Y. F., Zhang, M. Y., Hottiger, M. O., ... Sun, L. K. (2019). Baicalein attenuates pancreatic inflammatory injury through regulating MAPK, STAT3 and NF-κB activation. *International Immunopharmacology*, *72*, 204–210. doi:10.1016/j.intimp.2019.04.018 PMID:30999210

Qinghe, G., Guangyu, L., Xiaobin, L., & Qingsong, H. (2019). Baicalein exerts a protective role in pneumonia caused by *Streptococcus pneumoniae. Frontiers in Bioscience*, *24*(5), 849–858. doi:10.2741/4755 PMID:30844717

Rassias, D. J., & Weathers, P. J. (2019). Dried leaf *Artemisia annua* efficacy against non-small cell lung cancer. *Phytomedicine*, *52*, 247–253. doi:10.1016/j.phymed.2018.09.167 PMID:30599905

Ruan, J., Liu, Z., Qiu, F., Shi, H., & Wang, M. (2019). Simultaneous quantification of five sesquiterpene components after ultrasound extraction in *Artemisia annua* L. by an accurate and rapid UPLC-PDA assay. *Molecules*, *24*(8).

Scotece, M., Gomez, R., Conde, J., Lopez, V., Gomez-Reino, J. J., Lago, F., ... Gualillo, O. (2013). Oleocanthal inhibits proliferation and MIP-1α expression in human multiple myeloma cells. *Current Medicinal Chemistry*, *20*(19), 2467–2475. doi:10.2174/0929867311320190006 PMID:23521677

Siddique, A. B., Ayoub, N. M., Tajmim, A., Meyer, S. A., Hill, R. A., & El Sayed, K. A. (2019). (-)-Oleocanthal prevents breast cancer loco regional recurrence after primary tumour surgical excision and neoadjuvant targeted therapy in orthotropic nude mouse models. *Cancers (Basel)*, *11*(5), 637. doi:10.3390/cancers11050637 PMID:31072015

Tao, Z., Shi, A., Lu, C., Song, T., Zhang, Z., & Zhao, J. (2015). Breast cancer: Epidemiology and etiology. *Cell Biochemistry and Biophysics*, *72*(2), 333–338. doi:10.100712013-014-0459-6 PMID:25543329

Teklehaymanot, T., & Giday, M. (2007). Ethnobotanical study of medicinal plants used by people in Zegie Peninsula, Northwestern Ethiopia. *Journal of Ethnobiology and Ethnomedicine*, *3*(1), 12. doi:10.1186/1746-4269-3-12 PMID:17355645

Wang, F., Song, X., Ma, S., Liu, C., Sun, X., Wang, X., & Yu, Z. (2019). The treatment role of *Cyperus rotundus* L. to triple-negative breast cancer cells. *Bioscience Reports*, *39*(6), BSR20190502. doi:10.1042/BSR20190502 PMID:31123166

Wang, S., Zhu, Y., & Qiu, R. (2018). Shikonin protects H9C2 cardiomyocytes against hypoxia/reoxygenation injury through activation of PI3K/Akt signalling pathway. *Biomedicine and Pharmacotherapy*, *104*, 712–717. doi:10.1016/j.biopha.2018.04.144 PMID:29807220

Wang, Y., Hao, F., Nan, Y., Qu, L., Na, W., Jia, C., & Chen, X. (2018). PKM2 inhibitor shikonin overcomes the cisplatin resistance in bladder cancer by inducing necroptosis. *International Journal of Biological Sciences*, *14*(13), 1883–1891. doi:10.7150/ijbs.27854 PMID:30443191

Wu, Y. W., Tang, W., & Zuo, J. P. (2016). Development of artemisinin drugs in the treatment of autoimmune diseases. *Science Bulletin*, *61*(1), 37–41. doi:10.100711434-015-0975-9

Xu, X., Rajamanicham, V., Xu, S., Liu, Z., Yan, T., Liang, G., ... Wang, Y. (2019). Schisandrin A inhibits triple negative breast cancer cells by regulating Wnt/ER stress signalling pathway. *Biomedicine and Pharmacotherapy*, *115*, 108922. doi:10.1016/j.biopha.2019.108922 PMID:31048190

Yan, L., Xiong, C., Xu, P., Zhu, J., Yang, Z., Ren, H., & Luo, Q. (2019). Structural characterization and in vitro antitumor activity of a polysaccharide from *Artemisia annua* L. (Huang Huahao). *Carbohydrate Polymers*, *213*, 361–369. doi:10.1016/j.carbpol.2019.02.081 PMID:30879680

Yan, W., Ma, X., Zhao, X., & Zhang, S. (2018). Baicalein induces apoptosis and autophagy of breast cancer cells via inhibiting PI3K/AKT pathway in vivo and vitro. *Drug Design, Development and Therapy*, *12*, 3961–3972. doi:10.2147/DDDT.S181939 PMID:30510404

Yersal, O., & Barutca, S. (2014). Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World Journal of Clinical Oncology*, *5*(3), 412. doi:10.5306/wjco.v5.i3.412 PMID:25114856

Yin, H., Huang, L., Ouyang, T., & Chen, L. (2018). Baicalein improves liver inflammation in diabetic db/db mice by regulating HMGB1/TLR4/NF-κB signalling pathway. *International Immunopharmacology*, *55*, 55–62. doi:10.1016/j.intimp.2017.12.002 PMID:29223854

Zhang, H., Xie, B., Zhang, Z., Sheng, X., & Zhang, S. (2018). Tetrandrine suppresses cervical cancer growth by inducing apoptosis in vitro and in vivo. *Drug Design, Development and Therapy*, *13*, 119–127. doi:10.2147/DDDT.S187776 PMID:30587932

Zhao, H. M., Gao, Z. W., Xie, S. X., Han, X., & Sun, Q. S. (2019). Withaferin A attenuates ovalbumin induced airway inflammation. *Frontiers in Bioscience*, *24*(3), 576–596. doi:10.2741/4737 PMID:30468675

Zhao, Z., Jin, G., Ge, Y., & Guo, Z. (2019). Naringenin inhibits migration of breast cancer cells via inflammatory and apoptosis cell signaling pathways. *Inflammopharmacology*, *27*(5), 1021–1036. doi:10.100710787-018-00556-3 PMID:30941613

Zhao, Z., Liu, B., Sun, J., Lu, L., Liu, L., Qiu, J., ... Gong, W. (2019). Baicalein inhibits orthotopic human non- small cell lung cancer xenografts via Src/Id1 Pathway. *Evidence-Based Complementary and Alternative Medicine*, *2019*, 9806062. doi:10.1155/2019/9806062 PMID:30949224

Zhou, H. C., Wang, H., Shi, K., Li, J. M., Zong, Y., & Du, R. (2018). Hepatoprotective effect of baicalein against acetaminophen-induced acute liver injury in mice. *Molecules (Basel, Switzerland)*, *24*(1), 131. doi:10.3390/molecules24010131 PMID:30602693

Zito, P., Labbozzetta, M., Notarbartolo, M., Sajeva, M., & Poma, P. (2019). Essential oil of *Cyphostemma juttae* (Vitaceae): Chemical composition and antitumor mechanism in triple negative breast cancer cells. *PLoS One*, *14*(3), e0214594. doi:10.1371/journal.pone.0214594 PMID:30921428

Chapter 6
Anti-Ulcer Activities of Medicinal Plants and Natural Products

Madhu Rani
https://orcid.org/0000-0001-8759-6852
Deshbandhu College, University of Delhi, India

Rubina Chongtham
Deshbandhu College, University of Delhi, India

Ajeet Singh
https://orcid.org/0000-0002-4393-8889
National Dairy Research Institute, India

ABSTRACT

The peptic ulcer is a widespread and common health problem around the world. The major causes include generation of free radicles, decrease in mucosal defense factor, or increase in mucosal injurious factors. Various plants and their products have been known to prevent or reduce peptic ulcers. Natural products from plants are a rich resource used for centuries to cure different ailments. The use of phyto-constituents as drugs has proved to be clinically effective and less toxic than existing drugs. An attempt has been made to review some plant species and their products as phytomedicines showing promising results in prevention and treatment of peptic ulcers.

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INTRODUCTION

Peptic ulcer is very frequent gastrointestinal disorder stemming from an insufficient gastric mucosal guard. Many medications are accessible in the market as remedy for this disease; though, these medications are linked with troubling side effects. Peptic ulcer disease is represented by the disruption of the mucosal layer of the digestive tract. This term is encompassing a diverse group of conditions with ulcerations. It is amongst the most common gastrointestinal ailment affecting about 10-15% of the population. Ulcers primarily results from an imbalance among several endogenous antagonistic and defensive factors in the stomach, acid-pepsin secretion, like blood flow, mucus secretion, integrity of the mucosal barrier, cellular regeneration, growth factors and prostaglandins (Paguigan *et. al*., 2014). Other factors associated with occurrence of peptic ulcer include intake of alcohol, traumatic lifestyle, consumption of steroidal and non-steroidal anti-inflammatory medicines, bacterial infections (such as *Helicobacter pylori*), smoking, inferior socio-economic status and, occasionally, family history. Though, ulcer is not a fatal disease, it can be attributed to more severe complications as gastrointestinal perforations, internal bleeding, infiltration of ulcer into adjoining organs and gastric outlet impediment. Treatments available for peptic ulcer disease heal ulcerations, ease the pain and delay relapse of ulcerations. Generally, the medicines include antacids, antibiotics and proton pump inhibitors. Though different categories of medicines are used in the therapy of peptic ulcer, most of the drugs show significant side effects like arrhythmias, hypergastrinemia, haemopoetic changes, impotence, gynaecomastia and arthralgia. Medicaments from Ayurvedic or traditional medicinal system are an alternative approach.

This chapter aims to explore the anti-ulcer properties of some medicinal plants. A number of investigations have verified the efficacy of medicinal plants for the cure of peptic ulcer disease. The detected activity in such plants is accredited with the presence of various secondary metabolites including phenolic acids, terpenoids, flavonoids, tannins, alkaloids, and saponins. Studies revealed anti-ulcer activity of extract from numerous plants belonging to different families. Some of these plants are *Bauhinia* spp., *Eruca sativa* (Linn.) Cav. (Brassicaceae), *Gynura procumbens*, *Ocimum tnuiflorum*, *Toona ciliat, Diospyros* spp., *Symplocos* spp., *Chionanthus* spp., *Voacanga africana* Stapf (Apocyanaceae), *Palaquium ellipticum* Blanco (Sapotaceae), *Musa paradisiaca* Linn. (Musaceae), *Swietenia mahagoni* (Linn.) Jacq. (Meliaceae), *Wilbrandia ebracteata* Cong. (Curcubitaceae), *Xantolis tomentosa* Roxb. Raf. (Sapotaceae), *Calligonum somosum* Linn. (Polygonaceae) and *Pedalium murex* Linn. (Pedaliaceae). In this study, some of these plants are assessed for their anti-ulcer properties described in table 1 (Kokate *et al.,* 2007).

MEDICINAL PLANTS AND NATURAL PRODUCTS WITH ANTIULCER ACTIVITIES

Gynura Procumbens (Lour.) Merr. (Asteraceae)

The genus *Gynura* comprises of around 44 species. *G. procumbens* is traditionally used in many regions for the treatment of ailments like rashes, eruptive fever, migraines, kidney diseases, hypertension, viral skin diseases, diabetes mellitus, constipation, rheumatism and urinary tract infection (Afandi *et al*., 2014). A few of these traditional prerogatives have been corroborated in pharmacological studies, including use as anti-inflammatory, anti-hypertensive, anti-hyperglycemic, anti-herpes virus and anti-hyperlipidemic medicines. *G. procumbens* leaves extract showed a number of active chemical constituents including terpenoids, flavonoids, sterol glycosides, saponins and tannins. Mahmood *et al*., (2010) demonstrated anti-ulcerogenic activity by ethanolic extract of its leaves. They emphasized that it gave a gastro-protective effect in adult rats used in their study. Leaves of *G. procumbens* have shown to protect the gastric mucosa significantly against ethanol-induced injuries. The protection was found to be dose dependent, most prominent protection at a dose of 400 mg/kg as established by the reduction of ulcer zones in the gastric wall, reduction in the inhibition of edema and reduced leukocytes infiltration in the sub-mucosal layers (Mou & Dash, 2016).

Diospyros Malabarica (Desr.) Kostel. (Ebenaceae)

D. malabarica grows well all over India and other humid regions of the world. It is an evergreen tree with extensively branched, expanding crown. The bark, leaves, flowers and fruits of *D. malabarica* are used as ayurvedic herbal medicine to pacify burning sensation, diarrhea, inflammations, scalds, diabetes, hemorrhoids, skin diseases, leucorrhea, fever, kapha, vitiated pitta, splenomegali, anemia, burns and urinary tract infections. Young fruits contain tannin that are used for dyeing. Seeds are also used as medicine for curing chronic dysentery and diarrhea. In the indigenous system of medicine (Ayurveda), bark of *D. malabarica* is stated to be effective in the cure of gastric ulcers. Preliminary phytochemical investigations by Gopalakrishna *et al*., (2014) showed the presence of flavonoids, carbohydrates, proteins, steroids, tannins and glycosides in chloroform extract. Ande *et al*., (2012) postulated that flavonoids reduce histamine secretion from the mast cells. The reduction of histamine secretion may be attributed to inhibition of histidine decarboxylase enzyme and promoting biosynthesis of prostaglandin, which may be related to the anti-ulcer activity of flavonoids.

Musa Paradisiaca Linn. (Musaceace)

M. paradisiaca is a hybrid obtained by crossing *M. accuminata* and *M. balbisiana*. *M. paradisiaca* (banana) is the oldest cultivated plant with a wide range of therapeutic value. Its flowers are known to be used in therapy of dysentery, bronchitis, ulcers and diabetes. The sap of *M. paradisiaca* is used for the treatment of diseases like leprosy, epilepsy, hysteria, hemorrhage, fever, insect bites and digestive disorders. The seeds and roots are used for the treatment of digestive troubles. The pulp and peel of *M. paradisiaca* contain antifungal and antibiotic principles. It also contains norepinephrine, serotonin, and dopamine. Norepinephrine and dopamine results in blood pressure elevation, while serotonin prevents gastric secretion. Banana has been used as an antacid in the treatment of peptic ulcer because they protect the stomach from ulcers and ulcer damage. Banana forms a thick mucus barrier that protects from stomach acids and contains protease inhibitors that remove bacteria causing stomach ulcers. The active chemical constituents of *M. paradisiaca* include phytochemicals like flavonoids, phenols and glycosides. Different investigations reported various phytochemicals in different sections of banana. Many flavonoids and their related compounds have been isolated from the raw banana fruit, known as "plantain", like- leucocyanidin was isolated from the unripe pulp of plantain (Ragasa *et al*., 2007). Other compounds including tannin, norepinephrine, crystallizable and non-crystallizable sugars, tryptophan, indole compounds, starch, vitamin C, B-complex vitamins, iron, fats and mineral salts were also detected in the pulp of *M. paradisiaca* var. *sapientum* fruit by Ghani (2003).

Ehiowemwenguan *et al*., (2014) observed presence of certain secondary metabolites like saponins, glycosides, tannins alkaloids, volatile oil and flavonoids in the preliminary phytochemical screenings carried out on *M. paradisiaca* var. *sapientum* peels. The phytochemical screening with ethanol and methanol extracts of *M. paradisiaca* substantiated the occurrence of several secondary metabolites. Mallikarjuna *et al*., (2012) found alkaloids, steroids, tannins, glycosides, flavonoids, etc. in ethanolic extract, and xantho-proteins, alkaloids, saponins, and glycosides in methanol extracts.

Mahadeva *et al*., (2016) also reported presence of alkaloids, glycosides, flavonoids, saponins in *M. paradisiaca* tepal and skin extract. Aucubin, a glycoside present in *M. paradisiaca* possess antihistaminic activity and prevent the advancement of the ulcer.

Ocimum Tenuiflorum Linn. (Lamiaceae)

O. tenuiflorum (also known as *O. sanctum*) is a sacred plant and used in the therapy of a variety of ailments such as asthma, bronchitis, diarrhea, malaria, dysentery, skin diseases, arthritis, eye diseases, insect bites etc. It is used in preparation of many

delicacies around the world. Its dried leaves have been used as insect repellent in grain storages. The aromatic leaves and flowers are used in various forms including, decoction, tea and tincture. The infusions and decoction are considered to be stomachic and expectorant. The decoctions are used in common ailments like- bronchitis, coughs, diarrhea and skin diseases. These preparations are considered as prophylactic against epidemics like cholera, malaria and influenza. The seeds are considered as nourishing, antioxidant, mucilaginous and demulcent when taken with cow's milk, juice or water. They are used in treating lethargy, ulcers, weakness, vomiting and diarrhea. *O. sanctum* is considered as an overall tonic. The dried root powder taken in milk, ghee or as a decoction, is advocated for the treatment of malarial fever, as an analgesic, application to the insect bites and also to enhance sexual stamina and prevent premature ejaculation. Singh & Majumdar (1999) conducted a study on fixed oil of *O. sanctum* for the evaluation of the antiulcer activity. They concluded that it may possess significant ulcer protective activity. The ulcer protective effect may be attributed to the anti-secretory, anti-lipoxygenase and anti-histamine effect of the oil. The oil significantly reduces ulcer index in a dose related fashion. They also ascribed the inhibitory impact of fixed oil on gastric ulcer by 5-lipoxygenase pathway inhibition or leukotriene antagonistic action. Histamine-induced gastric ulcer occurs due to its vasospastic action and increased gastric acid secretion. The fixed oil of *O. sanctum* was reported to suppress histamine-induced vasospastic impact as well as gastric secretions.

Swietenia Mahagoni (Linn.) Jacq. (Meliaceae)

Many components of *S. mahagoni* tree have been utilized as traditional medication for the cure of various ailments including hypertension, malaria, cancer, amoebiasis, chest aches, fever, anemia diarrhea, dysentery and intestinal parasites (Maiti *et al*., 2007).

A number of phytochemical studies on *S. mahagoni* have managed to the extraction of more than 45 compounds belonging to the limonoids including the mexicanolide, andirobin, tetranortriterpenes, triterpens, gendunin, phragmalin and chlorgenic acid. Saad *et al.,* (2003) isolated eighteen tetranotriterpenoids from *S. mahagoni*, reported the presence of known fatty acids and terpenoids.

Eruca Sativa Mill. (Brassicaceae)

E. sativa is considered as medicinal plant with many reported properties like, tonic, laxative, digestive, anti-phlogistic, astringent, diuretic, emollient, rubefacient, stimulant, stomachic and anti-inflammatory for colitis. Young leaves are found to possess stimulant, diuretic, antiscorbutic and stomachic activity. *E. sativa* oil is used

to get rid of lice and dandruff, and against itching, urticaria (red weals on the skin which itch intensely), chilblains and scalds. It is also used in the lotion used to boost hair growth. It is sometimes used as antibiotic to treat infection of the respiratory and urinary tracts. Aqueous extracts of the plant tissues have shown herbicidal activity (Marwat *et al*., 2016; Nail *et al*., 2017).

E. sativa plant has 67 volatile compounds, signifying 96.52% of the total oil components. The oil contains both saturated and unsaturated fatty acids. Like other cruciferous vegetables, *E. sativa* contains health supporting phytochemicals involving flavonoids, isoflavonoids, polyphenols carotenoids and glucosinolates. Saleh *et al.,* (2016) observed in their study conducted on rats that ethanol leaf extract of *E. sativa* triggered increase of pH of gastric content and also production of mucus. Therefore, they determined that *E. sativa* exhibits an anti-ulcer activity by sustaining the acid-base balance of gastric contents. Similar observations were made by Bozokalfa *et al.,* (2011) in their study, sowing that *E. sativa* leaves possess a great quantity of vital mineral elements for human nutrition, primarily potassium, phosphorus and calcium. Some of these elements are believed to be involved in the anti-ulcer ability. Kim *et al.,* (2012) established in their study on role of selenium against gastric ulceration that it constrains the construction of ethanol-induced gastric mucosal lesions through the inhibition of lipid peroxidation and stimulation of enzymatic radical scavenging. Likewise, Chai (2011) inferred that bismuth containing compounds are frequently incorporated in the drug treatment programs for gastric ulcer and they are believed to damage the cell walls of ulcer causing bacteria *Helicobacter pylori*.

Adansonia Digitata Linn. (Malvaceae)

The chemical constituents of pulp of this plant contains phobaphenes, mucilage and gum, glucose, tartrate and acetate of potash, and other salts. The leaf contains wax, glucose, salts, gum, and albuminoids. The bark of this plant contains wax, soluble and insoluble tannin, acid gum, albuminous carbonate and chloride of sodium and potassium, and a glucoside adansonin.

Fresh juice of the leaves mixed with powdered ginger together with the expressed juice of the fresh root of Salvadora indica is applied with significant advantage to slothful syphilitic ulcer. Leaves of this plant are used as fomentations and poultices for irritable inflammatory ulcers (Nadkarni, 1976).

Allium Sativum Linn. (Liliaceae)

Mustard or coconut oil in which A. sativum has been fried is an excellent application for maggots infesting ulcers, ulcerated surfaces, and wounds. The juice of A. sativum

mixed with 3 or 4 portions of water has been used as a lotion for washing wounds and as well as foul ulcers (Nadkarni, 1976).

Aloe Vera (Linn.) Burm.f. (Liliaceae)

Leaves are being used successfully in America in the treatment of chronic ulcers. First the pain diminishes and after a few weeks the ulcers heal (Nadkarni, 1976). A. vera powder was mixed with gum acacia; the solution was administered orally in rats at dose of 200mg/kg against indomethacin induced gastric ulcer (Borra et al., 2011).

Annona Squamosa Linn. (Annonaceae)

A. squamosa is commonly known as "custard apple." It is cultivated in gardens all over India. Chemical constituents in this plant are alkaloids, flavonoids, saponins, and tannins. Seeds yield oil and resin; seeds, leaves, and immature fruit contain an acrid principle. Leaves made into a paste without adding water are applied to unhealthy ulcers (Nadkarni, 1976). The aqueous leaf extract protected against pylorus ligation and ethanol induced gastric ulcer in rats (Saleem et al., 2012).

Azadirachta Indica A. Juss. (Meliaceae)

A poultice of leaves mixed with sesamum seeds is useful in morbid ulcerations (Nadkarni, 1976). A. indica leaf extract protected against pylorus ligation and cold restraint stress induced gastric ulcer in rats (Divakar et al., 2001).

Balsamodendron Mukul (Arn.) Bhandari (Burseraceae)

B. mukul gum is mixed with lime juice or coconut oil; it is applied as a plaster or in the form of a lotion in indolent ulcers. Gum obtained from other species, B. pubescens found in Sind, Karachi, and Baluchistan, is used as ointment in bad ulcers such as Delhi sores, combined with sulphur, catechu, and borax (Nadkarni, 1976).

Bauhinia Variegata (Linn.) Benth. (Caesalpiniaceae)

The ethanolic and aqueous extract of root of B. variegate was administered at the doses of 200 and 400mg/kg orally, in rats against pylorus ligation, ethanol, and aspirin induced gastric ulcer. The extract significantly inhibited gastric mucosal damage and reduced the basal gastric acid secretion (Kumar & Rajani, 2011).

Berberis Aristata DC. (Berberidaceae)

Chemical constituents reported in the roots and wood of B. aristata are rich in a yellow alkaloid "berberine" bitter substance, which dissolves in acids and forms salts of the alkaloid; root contains two more alkaloids. The crude extracts known as rasaut (in Hindi) are prepared from the root; bark mixed with honey is useful to ulcerations of the skin (Nadkarni, 1976).

Beta Vulgaris Linn. (Chenopodiaceae)

Chemical constituents in B. vulgaris are an active principle "betin". A decoction of the root with a little vinegar is excellent for all kinds of ulcers and running sores (Nadkarni, 1976).

Carica Papaya Linn. (Caricaceae)

The ripe fruit is edible and unripe can be eaten cooked for indolent ulcer. The unripe fruit can be cooked as parts of salads, jellies, and stews although the ripe fruits are frequently eaten raw without the skin or seed. Intake of the unripe fruit of the plant has been linked with an antiulcer activity (Kottaimuthu, 2008). The aqueous seed extract of C. papaya was administered in rats against ethanol induced gastric ulcer (orally at the doses of 50 and 100mg/kg). The extract protected the gastric mucosa against ethanol effect. C. papaya extract significantly reduced the gastric juice volume and gastric acidity (Indran et al., 2008).

Euphorbia Neriifolia Linn. (Eurphorbiaceae)

E. neriifolia is commonly known as "common milk hedge" found in Central India and cultivated in Bengal (India). Chemical constituents in E. nerrifolia are euphorbon, resin, gum, caoutchouc, malate of calcium, and so forth. The plant juice is largely used with clarified or fresh butter as an application to unhealthy ulcers and scabies (Nadkarni, 1976).

Ficus Religiosa Linn. (Moraceae)

Chemical constituents of *F. religiosa* are bark containing tannin, caoutchouc and wax. Bark of this plant is useful in ulcers in decoction (simple kashayam) with a little honey (Nadkarni, 1976). The hydro alcoholic leaves extract of *F. religiosa* were studied at two dose levels (250 and 500 mg/kg, oral) in rats against absolute ethanol,

aspirin, and pylorus ligation induced gastric ulcer and significantly decreases the ulcer index value (Gregory *et al.,* 2013).

Galega Purpurea (Linn.) Pers. (Papilionaceae)

G. purpurea is commonly known as "purple tephrosia." It is found throughout India, especially in Southern India. It grows on hard stony ground too difficult to be rooted. Chemical constituents of G. purpurea yields gum, a trace of albumen and colouring matter, ash containing a trace of manganese, brown resin and chlorophyll and a principle allied to quercetin or querritrin, and glucoside rutin (Nadkarni, 1976).

Hibiscus Rosa Sinensis Linn. (Malvaceae)

The root of H. rosa sinensis is traditionally used for the treatment of ulcer among the kani tribes in Kanyakumari district, Tamil Nadu, India (Subitha et al., 2011). The aqueous and alcohol extracts of H. rosa sinensis roots possessed significant antiulcer activity in pylorus ligated rats (at the doses of 250 and 500mg/kg) and precisely proven that these extracts possess enough potential as an anti-ulcerogenic agent (Srivastava et al., 2013).

CONCLUSION

The plants and phytomedicines are important choice to treat peptic ulcer. Various phytochemicals including flavonoids, tannins, saponins, terpenoids showed their antiulcer activity. The activity is imparted due to their property as cryoprotection, antisecretory and antioxidants. The phytoconstituents also provide an insight in drug designing and biochemical action against ulcer causing conditions. We need to explore unapproached promising medicinal plants with the purpose to provide novel efficient and less toxic medicines for peptic ulcer.

Table 1. Medicinal plants with antiulcer activity

Sr. No.	Botanical name	Family	Parts used	Extract/ phytochemical	References
1.	*Gynura procumbens* (Lour.) Merr.	Asteraceae	Leaves	Ethanolic extract	Mahmood *et al.,* (2010)
2.	*Diospyros malabarica* (Desr.) Kostel	Ebenaceae	Fruits and Seeds	Tannins	Gopalakrishna *et al.,* (2014)
3.	*Musa paradisiaca* Linn.	Musaceae	Tepal and skin	Alkaloids, glycosides	Mahadeva *et al.,* (2016)
4.	*Ocimum tenuiflorum* Linn.	Lamiaceae	Fixed oil	-	Singh & Majumdar, (1999)
5.	*Eruca sativa* Mill.	Brassicaceae	Leaves	Ethanol extract	Saleh *et al.,* (2016)
6.	*Adansonia digitata* Linn.	Malvaceae	Leaves	Juice	Nadkarni, 1976
7.	*Aegle marmelos* (Linn.) Correa	Rutaceae	Fruit	-	Subitha *et al.,* (2011)
8.	*Allium sativum* (Linn.) Fam.	Liliaceae	Fruit	Aqueous juice	Nadkarni, 1976
9.	*Aloe vera* (Linn.) Burm. f.	Liliaceae	Whole plant	Plant powder mixed with gum acacia	Nadkarni, 1976
10.	*Annona squamosa* Linn.	Annonaceae	Leaves	Paste	Nadkarni, 1976
11.	*Azadirachta indica* A. Juss.	Meliaceae	Leaves	Aqueous extract	Divakar *et al.,* (2001)
12.	*Balsamodendron mukul* (Arn.) Bhandari	Burseraceae	Gum	-	Nadkarni, (1976)
13.	*Bauhinia variegata* Linn. (Benth.)	Caesalpiniaceae	Roots	Ethanolic and aqueous extracts	Kumar & Rajani, (2011)
14.	*Berberis aristata* DC.	Berberidaceae	Root and bark	Alkaloids	Nadkarni, (1976)
15.	*Beta vulgaris* Linn.	Chenopodiaceae	Root	Decoction	Nadkarni, (1976)
16.	*Carica papaya* Linn.	Cariacaceae	Seeds	Ethanolic and Aqueous extract	Indran *et al.,* (2008)
17.	*Euphorbia neriifolia* Linn.	Euphorbiaceae	Whole plant	Juice	Nadkarni, (1976)
18.	*Ficus religiosa* Linn.	Urticaceae	Leaves	Hydro-alcoholic extract	Gregory *et al.,* (2013)
19.	*Hibiscus rosa-sinensis* Linn.	Malvaceae	Roots	Aqueous and alcohol extract	Srivastava *et al.,* (2013)

REFERENCES

Afandi, A., Zulkiffli, H., Sadikun, A., & Ismail, S. (2014). Antioxidant properties of *Gynura procumbens* extracts and their inhibitory effects on two major human recombinant cytochrome P450S using a high throughput luminescence assay. *Asian Journal of Pharmaceutical and Clinical Research*, *7*(5), 36–41.

Ande, K.K., Gowrishankar, N.L., Manju Bhargavi, V., Nagarjuna, M., Rajani, G., Swetha, Y., & Vinay Reddy, P. (2012). Evaluation of antiulcer activity of ethanol extract of *Diospyros melanoxylon* (Roxb) Bark. *Int. J. Pharm. & Pharmaceu. Sc, 4*(4), 537-539.

Borra, S. K., Lagisetty, R. K., & Mallela, G. R. (2011). Anti-ulcer effect of *Aloe vera* in non-steroidal anti-inflammatory drug induced peptic ulcers in rats. *African Journal of Pharmacy and Pharmacology*, *5*(16), 1867–1871.

Botanical Survey of India/Flora of India. (n.d.). efloraindia.nic.in

Bozokalfa, K. M., Eşiyok, D., & Yağmur, B. (2011). Use of multivariate analysis in mineral accumulation of rocket (*Eruca sativa*) accessions. *Genetika*, *3*(3), 437–448. doi:10.2298/GENSR1103437B

Chai, J. (2011). *Peptic Ulcer Disease*. Rijeka, Croatia: Academic Press. doi:10.5772/749

Divakar, M. C., Rao, S. B., Nair, G. R. N., & Hisham, A. (2001). The role of fatty acids on the ulcer healing property of the nimbidin fraction of the neem oil. *Journal of Medicinal and Aromatic Plants Science*, *23*(3), 404–408.

Drenth, J., Jansonius, J. N., Koekoek, R., & Wolthers, B. G. (1971). The structure of papain. *Advances in Protein Chemistry*, *25*, 79–115. doi:10.1016/S0065-3233(08)60279-X PMID:4946704

Ehiowemwenguan, G., Emoghene, A. O., & Inetianbor, J. E. (2014). Antibacterial and phytochemical analysis of banana fruit peel. *IOSR Journal of Pharmacy*, *4*(8), 18–25. doi:10.9790/3013-0408018025

George, S. A., George, M., Joseph, L., & James, E. (2019). A Review on antiulcer, antidiabetic and hepatoprotective activity of *Ocimum sanctum* and *Musa paradisiacaInt. J. Pharm & Pharmaceu Res*. *Human Journals*, *15*(2), 70–76.

Ghani, A. (2003). *Medicinal plants of Bangladesh: Chemical constituents and uses* (2nd ed.). Dhaka, Bangladesh: The Asiatic Society of Bangladesh.

Gopalakrishna, C. H., Reddy, A. K., Sharief, N., Sushma, K. R., & Narendra, S. (2014). A study on anti-ulcer activity of *Diospyros malabarica* bark in ulcer induced rats. *International Journal for Pharmaceutical Research Scholars*, *3*(2), 375–381.

Gregory, M., Divya, B., Mary, R. A., Viji, M. H., Kalaichelvan, V. K., & Palanivel, V. (2013). Anti–ulcer activity of *Ficus religiosa* leaf ethanolic extract. *Asian Pacific Journal of Tropical Biomedicine*, *3*(7), 554–556. doi:10.1016/S2221-1691(13)60112-4 PMID:23836366

Indran, M., Mahmood, A. A., & Kuppusamy, U. R. (2008). Protective effect of *Carica papaya* L leaf extract against alcohol induced acute gastric damage and blood oxidative stress in rats. *The West Indian Medical Journal*, *57*(4), 323–326. PMID:19566009

Kim, J., Park, S. H., Nam, S. W., & Choi, Y. H. (2012). Gastroprotective effect of selenium on ethanol-induced gastric damage in rats. *International Journal of Molecular Sciences*, *13*(5), 5740–5750. doi:10.3390/ijms13055740 PMID:22754328

Kokate, C. K., Purohit, A. P., & Gokhale, S. B. (2007). *Pharmacognosy* (13th ed.). Pune: Nirali Prakashan Publisher.

Kottaimuthu, R. (2008). Ethnobotany of the Valaiyans of Karandamalai, Dindigul District, Tamil Nadu, India. *Ethnobotanical Leaflets*, (1), 24.

Kumar, K., Mruthunjaya, K., Kumar, S., & Mythreyi, R. (2013). Antiulcer activity of ethanol extract of the stem bark of *Careya arborea* Roxb. *International Current Pharmaceutical Journal*, *2*(3), 78–82. doi:10.3329/icpj.v2i3.13633

Kumar, Y. R., & Rajani, G. P. (2011). Analgesic and anti-ulcer activities of ethanol and aqueous extracts of root of *Bauhinia variegate* Linn. *International Journal of Pharmacology*, *7*(5), 616–622. doi:10.3923/ijp.2011.616.622

Li, D. D., Chen, J. H., Chen, Q., Chen, Q., Li, G. W., Yue, J. M., ... Shen, X. (2005). *Swietenia mahagony* extract shows agonistic activity to PPAR and gives ameliorative effects on diabetic db/db mice. *Acta Pharmacol*, *26*(2), 220–222. doi:10.1111/j.1745-7254.2005.00527.x PMID:15663902

Mahadeva, U. S., Ahmad, B. O., Mohd, K. S., & Zin, T. (2016). The Antiulcer activity of *Musa paradisiaca* (banana) tepal and skin extracts in ulcer induced albino mice. *The Malaysian Journal of Analytical Sciences*, *20*(5), 1203–1216. doi:10.17576/mjas-2016-2005-27

Mahmood, A. A., Mariod, A. A., Bayaty, F. A., & Wahab, S. I. A. (2010). An anti-ulcerogenic activity of *Gynura procumbens* leaf extract extracts against experimentally-induced gastric lesions in rats. *Journal of Medicinal Plants Research*, *4*(8), 685–691.

Maiti, A., Dewanjee, S., & Mandal, S. C. (2007). *In vivo* evaluation of antidiarrhoeal activity of the seed of *Swietenia macrophylla* King (Meliaceae). *Tropical Journal of Pharmaceutical Research*, *6*(2), 711–716. doi:10.4314/tjpr.v6i2.14650

Majid, M. A., Rahman, I. M. M., Shipar, M. A. H., Uddin, M. H., & Chowdhury, Y. R. (2004). Physico-chemical characterization, antimicrobial activity and toxicity analysis of *Swietenia mahagoni* seed oil. *International Journal of Agriculture and Biology*, *6*, 350–354.

Mallikarjuna, R., Prasad, S. H. K. R., & Jyothirmayi, N. (2012). Efficacy of ripened and unripened fruit extracts of *Musa X Paradisiaca L. (Bontha Cultivar)* against human pathogens. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(1), 457–458.

Marwat, S. K., Rehman, F., & Khan, A. A. (2016). Phytochemistry and pharmacological values of rocket (*Eruca sativa* Miller) - A review. *International Journal of Horticulture*, *6*(21), 1–7. doi:10.5376/ijh.2016.06.0016

Mou, K. M., & Dash, P. R. (2016). A comprehensive review on *Gynura procumbens* leaves. *Int J Pharmacognosy*, *3*(4), 167–174.

Nadkarni, K. M. (1976). *Indian Materia Medica* (Vol. 1). Mumbai, India: Popular Prakashan.

Nail, T. N. A., Ali, M. M., & Salim, E. R. A. (2017). Phytochemical studies on sudanese rocket (*Erucasativa*) seeds and oil constituents. *Am J Phytomedicine Clin Ther*, *5*, 1.

Paguigan, N. D., Castillo, D. H. B., & Chichioco-Hernandez, C. L. (2014). Anti-ulcer activity of leguminosae plants. *Arquivos de Gastroenterologia*, *51*(1), 64–68. doi:10.1590/S0004-28032014000100013 PMID:24760067

Pillai, N. R., & Santhakumari, G. (1984). Toxicity studies on nimbidin, a potential anti-ulcer drug. *Planta Medica*, *50*(2), 146–148. doi:10.1055-2007-969655 PMID:6473547

Ragasa, C. Y., Martinez, A., Chua, J. E. Y., & Rideout, J. A. (2007). A triterpene from *Musa errans. Philippine Journal of Science*, *136*(2), 167–171.

Saad, M., Iwagawa, T., Doe, M., & Nakatani, M. (2003). Swietenialides, novel ring D opened phragmalin limonoid orthoesters from *Swietenia mahogani* Jacq. *Tetrahedron*, *59*(40), 8027–8033. doi:10.1016/j.tet.2003.08.033

Saha, S., & Goswami, G. (2010). Study of antiulcer activity of *Ficus religiosa* L. on experimentally induced gastric ulcers in rats. *Asian Pacific Journal of Tropical Medicine*, *3*(10), 791–793. doi:10.1016/S1995-7645(10)60189-7

Saleem, T. M., Ramadurg, B., Kumar, R. P., Priyanka, N., Madhuri, M., Sravanti, U., & Sarala, K. (2012). Antiulcerogenic effect of aqueous extract of *Annona squamosa* Linn. *International Journal of Research in Phytochemistry & Pharmacology*, *2*(3), 157–159.

Saleh, M. M., Qader, S. W., & Thaker, A. A. (2016). Gastroprotective activity of *Eruca sativa* leaf extract on ethanol-induced gastric mucosal injury in *Rattus norvegicus*. *Jordan Journal of Biological Sciences*, *9*(1), 47–52. doi:10.12816/0027027

Singh, S., & Majumdar, D. K. (1999). Evaluation of the gastric antiulcer activity of fixed oil of *Ocimum sanctum* (Holy Basil). *Journal of Ethnopharmacology*, *65*(1), 13–19. doi:10.1016/S0378-8741(98)00142-1 PMID:10350365

Srivastava, S., Jaiswal, J., Gautam, H., Sharma, S., & Rao, C. V. (2013). Anti-ulcer activity of methanol extract of *Hibiscus rosa-sinensis* leaves. *International Journal of Pharmacy and Pharmaceutical Sciences*, *5*(3), 829–830.

Subitha, T. K., Ayyanar, M., Udayakumar, M., & Sekar, T. (2011). Ethnomedicinal plants used by Kani tribals in Pechiparai forests of Southern western Ghats, Tamil Nadu, India. *International Research Journal Plant Science*, *2*(12), 349–354.

Chapter 7
Cognitive Enhancement and Neuroprotective Abilities of Plants:
Ethnobotanical and Pharmacological Importance of These Plants

Kiran Mustafa
The Women University Multan, Pakistan

Javaria Kanwal
The Women University Multan, Pakistan

Samia Khakwani
The Women University Multan, Pakistan

Sara Musaddiq
The Women University Multan, Pakistan

ABSTRACT

Extensive research suggests that a number of plant-derived chemicals and traditional Oriental herbal remedies possess cognition-enhancing properties. Widely used current treatments for dementia include extracts of Ginkgo biloba and several alkaloidal, and therefore toxic, plant-derived cholinergic agents. Several non-toxic, European herbal species have pan-cultural traditions as treatments for cognitive deficits, including those associated with aging. Acute administration has also been found to reliably improve mnemonic performance in healthy young and elderly

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cohorts, whilst a chronic regime has been shown to attenuate cognitive declines in sufferers from Alzheimer's disease. The present chapter looks at the ethnobotanical and pharmacological importance of various plants cognitive enhancing and other neuroprotective abilities.

INTRODUCTION

Gradual loss of function or structure of the nerve cells lead to the neurodegenerative disorders such as Parkinson disease, Alzheimer disease and Huntington's disease, multiple scleroses etc. According to World Health Organization (WHO), the second principal cause of death will be neurodegenerative diseases by the year 2040 (Tejada *et al*., 2017). Recently immense focused has been placed on understanding the mechanism of death of nerve cells. Neurotic injuries are associated with the series of neural toxic agents including inflammatory cytokines, mitochondrial malfunctioned, oxidative stress and irregular protein activities (Ansari & Khodagholi, 2013; Chen *et al.,* 2016; Hirsch & Hunot, 2009). One of the leading reasons behind neuron death is reactive oxygen species (ROS) that induced oxidative harm to protein, lipids and DNA followed by persuading oxidative strain. Besides this oxidative stress is predominantly associated with death of secondary cells in various central nervous system ailments (Jalsrai *et al.,* 2016; Sultana & Butterfield, 2010). Recent analysis has shown that neuron death is occurred by apoptosis. There are two major signaling pathways that participated in the apoptotic cell death; mitochondrial pathway (intrinsic) and death of receptors (extrinsic) (Elmore, 2007). Different transcription factors are involved in neuron protection, such as cAMP-response element binding protein, nuclear factor erythroid-derived 2, nuclear-factor-kappa-B etc. These transcriptional agents are primarily linked with regulation of various genes that modulate the inflammatory action and activation of antioxidant enzyme (Ansari *et al.,* 2011; Ashabi *et al.,* 2012). Additionally, transcription factors are because of their functions in growth of nerve cells, synaptic plasticity, axonogenesis, and neuronal homeostasis (Freese *et al.,*2010). In this context, neuroprotective elements appeared as a shielding agent to secure CNS against disorders associated to neuron (Pak *et al.,* 2016). Various synthetic drugs are present for neurodegenerative disorders like acetylcholinesterase blockers, neuroleptic drugs, dopamine therapy, brain stimulation, antipsychotic drugs (Mizuno, 2014) non-steroidal anti-inflammatory drugs and riluzole etc. (Chen & Pan, 2014). These drugs are useful against several neurodegenerative diseases but possess

severe side-effects in longer run. Additionally, the present medication only treats the patient symptomatically. Thereby, to cope with the problem of neurodegenerative ailments, multifunctional, secure and extremely efficacious drugs must be developed. For the last few decades, significant amount of research has done on development of drugs for neurodegenerative diseases from the natural products particularly plants. The phytochemicals obtained from the plants have exhibited remarkable cognitive enhancement and neuroprotective abilities (Crane, 2009; Desai & Grossberg, 2005). In this chapter, pharmaceutical and ethnobotanical significance of plants with cognition functioning and other neuroprotective potentials have been described.

Bacopa Monniera (Linn.) Pennell (Plantaqinaceae)

B. monniera is native to India and has been utilized for the treatment of several diseases involving stress, memory loss and intellect. It generally consists of saponins and alkaloids. The major active components regarding the enhancement of cognitive abilities are saponins bacoside A and B. In rats, B. monniera considerably improves the memory, and hindered the amnesic effects caused by electric shock, immobilization stress and scopolamine. Additionally, B. monnieri has been found to improve protein kinase action in the hippocampus region, which could also contribute to its nootropic action. Simultaneously administration of brahmi and phenytoin for 15 days delays the phenytoin stimulated disabilityin rats. For 15 days, internal intakes of B. monniera product lead to enhance acetylcholine along with the reduction in activity of choline acetylase. The administration of the herb also reduced the colchicine induced cholinergic and muscarinic receptor binding in the hippocampus and frontal cortex of the rats (Russo & Borrelli, 2005; Williamson, 2002).

Nardostachys Jatamansi (D.Don) D.C. (Caprifoliaceae)

N. jatamansi is native to India, China and Nepal. In India this plants has been recommended since 800 B.C. for variety of diseases such as epilepsy, cholera, neurosis, hysteria, convulsive ailments and palpitations. In traditional medicine system, *N. jatamansi* is used for promoting sleep, energizing the mind, alleviation of mental ailments and as a brain tonic. All parts of the plant including rhizomes and roots have miscellaneous medicinal qualities, the major component i.e. jatamansone is present in rhizomes. *N. Jatamansi* is enriched with variety of chemical constituents such as volatile essential oil, sesquiterpenes (like jatamansone and valeranone) and coumarins (Rahman *et al.,* 2011).

In a study *N. jatamansi* extract with methanol and water was analyzed separately for acetyl cholinesterase inhibition, the extract with methanol exhibited better results. The tests of passive avoidance paradigm and elevated plus maze were used

to estimate the memory and learning of young and aged rats after the continuous oral administration of *N. Jatamansi* extract. The extract was made with ethanol as solvent and given in different dosage for 8 days. The dosage of 200 mg/kg remarkably enhance memory and learning of the rats along with the depletion in hyoscine and diazepam induced amnesia. Additionally, the extract was found effective against age related amnesia. Thus, *N. jatamansi* might be proven effective against dementia in older patients (Vinutha, 2007).

Convolvulus Pluricaulis Choisy (Convolvulaceae)

In Ayurveda, *C. pluricaulis* used as drug, for cognitive enhancement. It is described as powerful brain tonic both singly and with the combination of other herbs. The plant is also regarded as the remarkable brain and nerve stimulator in Ayurvedic medicine. According to Ayurvedic Pharmacopoeia of India, whole plant of *C. pluricaulis* along with *C. pluricaulis*, other plants like *Clitoria ternatea* Linn., *Evolvulus alsinnoides* Linn. and *Canscora decussata* Lam. have been frequently employed in herbal formulations for cognitive enhancement. Shankhpushpi is the major constituent of the local formulations like shankhavali churna, shankhpushpi syrup and dimagheen etc. All of them are recommended as brain tonics in traditional medicine system of India (Mudgal, 1975; Nahata *et al.,* 2008). *C. pluricaulis* extract with ethanol, ethyl acetate and water, exhibited excellent memory improving abilities. The tests of passive avoidance paradigm and elevated plus maze were used to estimate the memory and learning enhancement of the lab rats after the administration of C. *pluricaulis* extract. The results indicated that the extract have remarkable effects on knowledge and memory enhancement (Nahata *et al.,* 2010).

Huperzia Serrata (Thunb. Ex Murray) Trevis (Lycopodiaceae)

In the traditional Chinese medicines system *H. serrata* is extremely useful for enhancing blood flow and reducing the problems of memory loss. In Chinese medicine herbal formula "Qian Ceng Ta", the major constituent of the product is club moss, *H. serrata* and is reported to enhance cognition abilities, activity of motor neurons and facilitation of the memory. Thus, it is prescribed to patients of multi-infarct dementia and Alzheimers disease (Howes & Houghton, 2003). An alkaloid huperzine A is obtained from *H. serrata,* functions as an acetylcholinesterase blocker and an anti-neurotoxic agent. Huperzine-A has shown anti-neurotoxic action against â amyloid peptide of 25–53 amino acids, glucose oxygen destitution and against cytotoxic action of free radicals. Huperzine-A alleviates the apoptosis by blocking the mitochondria-caspase (cysteine, aspartic, proteases) passage way. In synaptic membranes and in cortex, it hampered toxic action that is induced

by N-methyl-d-aspartate (NMDA).The reason for this is that in central nervous system, huperzine A increases acetylcholine concentration (which leads to the cholinergic neurotransmission) approximately 100 times more than compared with tacrine used for the treatment of Alzheimer disease (Huang, 1998). In a study 400g of huperzine-A was given to 100 patients for 3 months proved to be choosy for acetylcholinesterase as compared to butyrylcholinesterase (BuChE). Moreover, it was harmless as compared to laboratory prepared acetylcholinesterase blockers i.e. tacrine and donepezil. Unhappily, huperzine-A is highly associated with risk of dysentery, nausea, vomiting, and muscle spasms. Cholinergic agent may also have chances of miscellaneous disorders viz. heart dysrhythmia, pulmonary and peptic ulcer (Anekonda & Reddy, 2005).

Ginseng Ginseng Oken (Baill.) (*Araliaceae*)

Ginseng is actually the roots of multifold species of plant belonging to genus Panax. One of them is *P. ginseng*. It is frequently consumed and well known with the ginseng. It is native to the East Asia especially Korea and China. Roots of ginseng getting the age of 3-6 years are cultivated in China and then refer to drying and are roughly known as white ginseng. After being harvested, it refer to steam and roughly known as red ginseng. It is interesting that, after being treated with both these techniques, various products of ginseng show diverse actions owing to the various amount of saponins (Liao *et al.,* 2002).

Both ginseng and ginsenosides as a major element of ginseng considered to be important, as they have useful impacts on samples of degenerative disorder of neuron. In rodents, agent that stimulate Parkinson like 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and its energetic metabolic product such as 1- methyl-4-phenylpyridinium (MPP+) believed to be poison and their effects can be nullified by long term oral intake ginseng extract that refer to G115. Likewise, striatal dopamine transporter (DAT) was notably shielded credited to ginseng remedy. After being subjective to either glutamate or MPP+, ginsenosides i.e. Rb1 and Rg1 enhance the viability of basic cultured cells of dopamine and boosted their growth in terms of its nutritional value (Benishin, 1992). Ginseng mainly consists of ginsenosides i.e. Rb1 and Rg1 which regulate acetylcholine discharge and recapture the different choline ingestion area, particularly in the hippocampus. In brain of rodents, it enhances choline acetyltransferase stage. It is concluded that ginsenosides may enhance focal cholinergic working in humans and may be consumed to cure memory loss. It has been described as well, in the cerebral cortex, ginsenosides upgraded the level of norepinephrine and dopamine, elucidated the compatible action of ginseng extract including cognitive development, consciousness, unsegregated sensory-motor

working, and time to response auditory stimuli time in healthy volunteer (Houghton & Howes, 2005).

Ginkgo Biloba Linn. (*Ginkgoacaeae*)

The leaf extract of *G. biloba* is seen to be important as it is bestselling medicinal product of Europe and have been used to cure sign of initial phase of Alzheimer's ailment, cramping pain, vascular dementia and tinnitus of vascular origin. Egb-761 refers to standardized extract of plant, *G. biloba*. In US, ginkgo is categorized as a nutritional additive; Ginkai, Ginkoba and Ginkgold are seen to be American trademark exposed to medical research in comparison of extract of *G. biloba* (Blumenthal *et al.,* 2000). It involves many and other biological actions such as endothelial inactivity brought about by retardation of 3', 5'-cyclic GMP phospho-diesterase, retardation of muscarinergic adrenoceptors and cholinoceptors declines associated with age and forces the choline to intake in hippocampus. Extract of Ginkgo lead to retardation of beta-amyloid discharge (Watanabe *et al.,* 2001).

Research analysis of minimum 6 months span exposed that extract of ginkgo and second-level cholinesterase blockers were equitably efficacious to cure light to modest disease of Alzheimer's dementia (Kleijnen & Knipschild, 1992). Dimensional evaluation on 33 cases by Cochrane organization exposed that ginkgo appear to be important in reference to its safety and medicinal values i.e. favorably proved to enhance cognition qualities. Although, the three noval cases exposed incongruous outcomes proposing that substantial case with new technique is demanded to respond to questions about remedial impacts (Birks & Evans, 2009). Several case reports of bleeding complications associated with ginkgo use include subdural hematoma, subarachnoid hemorrhage, intracerebral hemorrhage, and hyphema; the causality of these events has not been established. In multifold cases, bleeding difficulties due to ginkgo application are highly associated with risk of subarachnoid hemorrhage, cerebral bleeding, hyphema and subdural hematoma, but reasons behind these diseases are unknown. The undressed leaves of ginkgo mainly stuffed with ginkgolic acids that thought to be poisonous. Owing to allergic nature of ginkgo formulation, it is opposition in its use. Ginkgo is highly compatible, but has adverse effects that are being infrequent, generally moderate involving dysentery, nausea, vomiting, and increase in heart beat rate, head pain, anxiety, frailty and reddening of skin. However, no analysis has been done in reference to limitation on consumption of ginkgo especially in phase of lactation and pregnancy, it appears careful not to take ginkgo in case of deficiency of any information. Moreover, 120 to 240 mg of ginkgo in form of 2-3 dose is regularly recommended to the sufferer from dementia and memory issues (Kim *et al.,*1998; Mizumaki *et al.,* 2002)

Paenoia Suffruticosa Andrews (Paeoniaceae)

Moutan cortex is the root bark of *P. suffruticosa* usually stuffed with major element Penta-O-galloyl-beta-d-glucopyranose (PGG) that hampers-Aβ fiber development and subverts prefabricated Aβ fiber depending on amount. Over and above, *P. suffruticosa* boosted long standing memory loss in mouse undergoing an Alzheimer's disease and arrest Aβ collection in brains of processed female rat (Fujiwara *et al.,* 2009). In conventional Chinese medicinal system, Moutan cortex is believed to be highly resistive in case of inflammation and diseases related to fever (Hsieh *et al.,* 2009). Additionally, it has shown biological action against mutagen, oxidant and proliferative agent. Previously, it was described that PGG provides safety to neuron from physiological strain by stimulation of HO-1 gene visibility (Choi *et al.,* 2002).

Polygala Tenuifolia Will. (Polygaloceae)

According to conventional Chinese system of medicine, roots of *P. tenuifolia* acts as a brain and heart stimulant, neuroleptic and neurotic agent. Moreover, it is consumed for treatment of sleeplessness, memory impairment and neuritis. In Chinese pharmacological medicine, the roots believed to be valuable in reference to mental strength and resolution i.e. enhancing remembrance and perception. Several studies showed the roots of *P. tenuifolia* having alleged memory improving power, some of which emphasis on conventional Chinese formulation i.e. DX-9368. DX-9368 is an herbal product mainly stuffed with *Acorus gramineus, Panax ginseng, P. cocos* and *P. tenuifolia*. Over and above, it has presented promising results with regard to symptoms of Alzheimer's disorders in many models involving animals. DX-9386 boosted motor action, make memory loss better, minimized peroxidation of lipids, and extended the life duration in female rat and, improved the amnesic effect in female rat credited to scopolamine and ethanol (Nishiyama *et al.,* 1994).

In rats, root extract of *P. tenuifolia* has been change the cognitive loss thanked to scopolamine. Furthermore, it acts as a antineurotoxic agent that is highly resistive to innocuous metabolic products of APP and glutamate, and it retarded the acetylcholinesterase action in a dose related manner (Park *et al.,* 2002). *P. tenuifolia* discharge polygalasaponins well-known to contain dopamine and 5-hydroxytryptaminereceptor adverse action, so have been prescribed to psychosis patient (Chung *et al.,* 2002).

Tenuifolin is a crude extract derived from *P. tenuifolia*. An unrefined extract freed from *P. tenuifolia* was probably lead to retardation of beta-site amyloid precursor protein (APP) cleaving enzyme followed by reducing of Aβ discharge from transfected cells. Although, after being treated with extract of *P. tenuifolia*, synaptic impairment and dendrite deterioration stimulated by Aβ25–35 were not

cured. Unlike, extract of *P. tenuifolia* totally retarded the Aβ25–35 action for the stimulation of cell impairment. According to conventional medicinal system of Japanese and Chinese, *P. tenuifolia* is ideally reported as a drug to treat dimentic patient (Naito & Tohda, 2006). It has also been reported that *P. tenuifolia* upgraded those memory and learning actions that occur due to the hippocampus through improvement of synaptic transmission, stimulation of the mutagen activated protein kinase cascade, enhancement in transmission of synapsis and improvement in brain derived neurotrophic factor (BDNF) phase derived from brain (Xue *et al.,* 2009). Moreover, owing to long term strain, *P. tenuifolia* stimulated the visibility of BDNF and TrkB mRNA to enhance healing of nerve cell from impairment. *P. tenuifolia* extract with ethanol releases methanolic portion presenting neuroprotective action persuaded by serum and glutamate deficit in pheochromocytomma-12 cells (Li *et al.,* 2008). Moreover, elements such as esters and oligosaccharide found in *P. tenuifolia* showed potent *in vitro* antioxidatnt action in aging-improved female rat (Liu *et al.,* 2010).

Cassia Obtisufolia (Linn.) H. S. Irwin. and Barneby. (Fabaceae)

In conventional eastern system of medicine, *C. obtisufolia seeds* have been frequently consumed. Lately, its seed extract with ethanol have been found to cause memory loss in female rat. *C. obtusfolia* seed discharge gluco-obtusifolin-L and its aglycone and obtusifolin retard acetylcholinesterase action *in-vivo* and *ex-vitro* (Kim *et al.,* 2009). Extract of *C. obtisufolia reduced* calcium disturbance and boosted mitochondrial safety in chief cultured hippocampus of mouse. Although, extract of *C. obtisufolia* have shown no action on death of cell stimulated by development effect on cell death induced by incubation with oligomer in form of Aβ (Drever *et al.,* 2008). Though, research also show the anti-heptaprotective action associated with *C. obtisufolia* in sufferer of ancient hepatitis B (Yuen *et al.,* 2006).

Lycium Barbarum Linn. (Solanaceae)

L. barbarum, is familiar owing to its potent biological action. As, in Asian countries, it is highly resistive to aging and provide the defence to eyes. *In vivo* analysis shown that *L. barbarum* extract used for preconditioning of cortical neuron minimize *the* lactate dehydrogenase discharge in rat. Besides this, extract of *L. barbarum* alleviated Aβ peptide-activated caspases-3-like action followed by minimized phosphorylation of c-Jan NH-2-terminal kinase-1 (JNK-1) and its substrates c-Jun (Yu *et al.,* 2005). Lately, It was identified that *L. barbarum* mainly filled with polysaccharides that acts as an protective agent for Aβ and non-proteinogenic α-amino acid (Ho *et al.,* 2010).

Uncaria Rhynchophylla (Miq.) Jacks. (Rubiaceae)

In conventional Chinese system of medicine, *U. rhynchophylla* considered to be important as it has medicinal value to treat spasmodic, heart and central nervous system disorders (Chou *et al.,* 2009; Lee *et al.,* 2003). *U. rhynchophylla* is generally packed with important elements such as uncarinic acids-C and D and triterpene esters (Umeyama *et al.,* 2010). *U. rhynchophylla* also consists of alkaloids have impacts on heart and brain involving irregular heartbeat, high blood pressure, cardiac dysrhythmia and shielded from cerebral infraction. It involves mechanisms for normal functioning viz. inhibition of calcium passages, activation of potassium passages, and modulating of nerve transmitter transfer and metabolic reaction (Shi *et al.,* 2003). Moreover, *U. rhynchophylla* also arrested-Jun N-terminal kinase phosphorylation (Hsieh *et al.,* 2009). *U. rhynchophylla* significantly inhibited NMDA receptor-activated ion currents in acutely dissociated hippocampal CA1 neurons in cultured brain slices (Lee *et al.,* 2003). *U. rhynchophylla* thoroughly retarded Aβ assembly and notably damage pre-designed Aβ1–40 and Aβ1–42 fibers that is credited to Alzheimer's disorder (Fujiwara *et al*., 2006).

Murraya Koenigii (Linn.) Sprengel (Rutaceae)

M. koenigii is well known with the term "curry patta". For many times, its leaves have been regularly consumed as a liked spice in dishes of India. Nutriment consisting of *M. koenigi* leaves notably enhance memory level and decreased memory impairment with dosage concentration stimulated by hyoscine and diazepam in juvenile and elderly female rat (Vasudevan & Parle, 2009). More and above, *M. koenigii* degraded the cholesterol level and cholinesterase action in brain. *M. koenigi* leaves considered to be important in reference to its medicinal value. As it is highly resistive (in Ayurveda) to microbes, inflammatory, heptatoxic and hypercholesterolemic agents (Birari *et al.,* 2010).

Centella Asiatica (Linn.) Urban (Apiaceae)

In Sri Lanka, *C. asiatica* is utilized as leafy vegetables. In addition to this, it has antianxietic property and also functions as a brain stimulant (Bradwejn *et al.,* 2000). Recent analysis present that, in rat, *C. asiatica* extract with water is efficacious to arrest cognitive declines and physiological strain credited to delivery of streptozotocin into cerebral lateral ventricles (Veerendra Kumar & Gupta, 2003). Following research on malignancy of neural crest cell exposing Aβ, that in its turn, recognized the ERK/RSK signaling passage participated in a feasible molecular mechanism for memory upgrading action of Gotu Kola extract (Xu *et al.,* 2008). Lately, extract of *C. asiatica*

electively reduced amyloid β of hippocampus in mouse suffer from Alzheimer's exposing variation in Swedish' APP and the M146L presenilin 1 (Dhanasekaran *et al.,* 2009).

Desmodium Gangeticum (Linn.) D.C. (Fabaceae)

D. gangeticum is frequently utilized for the cure-ness of CNS diseases in traditional medicinal system. In female rat, *D. gangeticum* extract with water considerably enhance knowledge and reminiscence. Furthermore, it thought to be depleted the memory impairment thanked to spontaneous aging and scopolamine drug. It is also noted that, *D. gangeticum* extract diminished the total acetylcholinesterase action in brain (Joshi & Parle, 2006).

Biota Orientalis (Linn.) Franco (Cupressaceae)

In conventional medicinal system of China, *B. orientalis* is medicinally consumed to treat sleeplessness and memory loss. In female rat, polyherbal products in formulation (S-113m) of *P. ginseng*, *B. orientalis* and *Schisandra chinensis* selectively enhance memory score and severance. The seed of *B. orientalis* extract improved the memory-attainment diseases persuaded by amygdala and basic forebrain abrasion as well (Nishiyama *et al.,* 1995)

Clitoria Ternatea Linn. (Fabaceae)

The roots of the Indian medicinal plant *C. ternatea* have a reputation for promoting intellect. *C. ternatea roots* have importance to raise. It is observed that, these demonstrable outcomes may be associated with the result of cholinergic action of central nervous system. Research analysis on airy organs and roots of *C. ternatea* present that, in rat, alcoholic extracts of roots is thought to be efficacious for reducing memory impairment then compared with extract of airy organ of plant. Boosted memory maintenance after oral intake of root extract of *C. ternatea* was related with promoting amount of choline acetyltransferase and acetylcholine in brain of rat, but not related with retardation action of acetylcholinesterase, and action of cortical acetylcholinesterase is seen to be enhanced (Taranalli & Cheeramkuzhy, 2000). Oral intake of root extract grind with water solvent enhance the acetylcholine in hippocampus of rat and it was also imagined hypothesized that this is edited to enhanced acetylcholine synthetic enzymes (Rai *et al.,* 2002). In mice, *C. ternatea* extract of fruits, flowers, stem, and leaves collected with alcohol has the property of neuroleptic agent, but it was not noted that which specific organ is participated for sedative result. So, specific organ responsible for sedative action is still unknown.

More and more analysis was required to expose reaction mechanisms for the noted outcome of root extract and the compound participated for this action (Kulkarni *et al.,* 1988).

Curcuma Longa Linn. (Zingiberaceae)

In traditional system of India, it is known as "asayana". It is also well known with the term turmeric in English. Rhizomes of *C. longa* releases curcuminoid that has also been considered as a focal point in reference to research. Specially, research analysis shows that curcuminoids are highly resistive to oxidant and inflammation action but cognitive ailments and medical outcomes are not of main concern. Additionally, aside from curcuminoid, biologically potent compounds freed from *C. longa* attributed the attention towards the conventional application of herb. In vitro study show that curcumin acts as a neurotoxic agent against brain trauma that is persuade by oral intake of ethanol. As a result of this, some changes occurred viz. peroxide level of lipids is minimized and glutathione is enhanced (Rajakrishnan *et al.,* 1999). *In vitro* analysis also disclosed that compounds like demethoxycurcumin, bisdemethoxycurcumin, curcumin and calebin-A released from *C. longa* have been used to shield pheochromocytoma cells-12 from βA insult, this action was also proposed in view to antioxidant outcomes (Kim *et al.,* 2001). Another action is anti-depressive may be related to the governance of signs of ailment associated with cognition. After being taking orally, *C. longa* with water extract showed anti-depressive action related with retardation of monoamine oxidase of brain (Yu *et al.,* 2002).

Lycoris Radiata (L'Her.) Herb. (Amaryllidaceae)

A medicinal herb, *L. radiata,* releases galantamine that is known as an amaryllidaceae alkaloid (Bores et al., 1996). In Europe, galantamine is authorized for therapy of Alzheimer's disorder. In clinical trials, internally in taken of galantamine proved to be highly compatible for the treatment of Alzheimer's and notably enhance cognitive role (Wilkinson *et al.,*. 2001). Galantamine considered to be important as it induce receptor of nicotine (Pearson, 2001) in its turn, it boosted the memory and cholinergic action. Moreover, it is proposed that galantamine have beneficial health effect upon other acetylcholinesterase blockers. *L. radiata* also discharge another alkaloid lycoramine that is highly resistive to cholinesterase action (Irwin & Smith, 1960).

Magnolia Officinalis Rehder & Wilson (Magnoliaceae)

In conventional Chinese system of medicine, the root bark and *M. officinalis* stem has been consumed to arrest nervousness and mental illness. Studies showed that *M. officinalis* extracts and its liberated compounds have been consumed to endorse the alleged actions. Magnolol, honokiol and *M. officinalis* discharge ligands i.e. biphenole that are of main concern. Invitro research shown one of the conventional Chinese formulations familiar with the terms "Banxia Houpu" mainly packed with *Poria cocos*, *Zinziber officinale*, *Pinellia ternata* and *M. officinalis*. Banxia Houpu prescription show potent biological action i.e. antidepressive action (Luo *et al.,* 2000). In general, in order to demonstrate alleged results of *M. officinalis*, along with medicines of 'antidementia', other actions related to cholinergic role have been elucidated. In vitro examination present that magnolol and Honokiol enhancecholine acetyltransferase action and retardedscrelease (Hou *et al.,* 2000). Other actions associated with causes of Alzheimer's disorder have also been pinpointed. The anti-anxiety results in view to magnolol and honokiol may be associated with symptomatically control of Alzheimer's disorder, have been credited to their potential to enhance GABAergic transport of neurons (Squires *et al.,* 1999).

Salvia Miltiorrhiza Bunge (Lamiaceae)

Historically, *S. miltiorrhiza* contain to have application as therapies of miscellaneous health problems. To cope with the diseases of blood, red dehydrated roots of *S. miltiorrhiza* have been frequently consumed. In conventional Chinese system of medicine, it is suggested to settle the heart down and appease the nerves (Huang, 1993). Formal reasons behind the use of roots refer to its medicinal value to treat diseases involving sleeplessness, blood flow disease, neurasthenia and relief the swelling (Tang & Eisenbrand, 2013).

S. miltiorrhiza is also familiar with the term "Chinese sage" and has been the matter of complete research and thus, multiple biological actions perhaps associated with diseases of central nervous system including Alzheimer's disease, have been pinpointed. In order to cure cerebrovascular disorder, this plant is thought to be highly effective. Moreover, special attention has been paid to search out feasible process for the defensive action of *S. miltiorrhiza* to treat brain ischaemia. Malfunction of a neuropeptide, VIP is disseminated in alimentary canal and central nervous system, has been reduced through roots of *S. miltiorrhiza* that perhaps involve in alternation in brain ischemia (Kuang & Xang,1989).

Apportioning deviation of neuropeptide substance P may participated in diseases of central nervous system viz. Alzheimer. Brain disorder like Alzheimer is credited to low level of neuropeptide substance (Quigley & Kowall, 1991) and have been

prescribed in case of neuron impairment followed by brain ischemia, roots of *S. miltiorrhiza* also has shielding effect in condition of ischemia (Kuang *et al.,* 1991), and perhaps involve in treatment of diseases associated with central nervous system. Roots of this plant retarded the death of cell i.e. neuron followed by retardation of glutamate discharge from presynaptic neuron (Kuang & Xiang, 1994); In Alzheimer's disorder, regulation of glutamatergic action is now identified as a remedial object. It is also proposed that retardation of nitric oxide (NO) synthesis demonstrated the central nervous system shielded action noted with roots of miltiorrhiza (Kuang *et al.,* 1996). It is thought that pharmaceutical application of NO proposed the results of stimulating amino acid involving their results on development of brain, remembrance and learning. (Moncada, 1991).

Melissa Officinalis Linn. (Lamiaceae)

Conventionally, *M. officinalis* has frequently been consumed in view to its upshots on Central nervous system. *M. officinalis* extract with water and methanol have been employed to examine defensive action on cell line of pheochromocytoma-12, free hydrogen peroxiradical scavenging features and neural biological action, retardation of monoamine oxidase, acetylhydrolyase enzymes and liking with receptors of GABAA-benzodiazepine receptors. Research analysis shown that *M. officinalis* considered to be valuable in view to defensive action on hydrogen peroxide stimulate noxiousness in pheochromocytoma-12 cells. In cells and without cell system, the radical scavenging characteristic was examined as well. Along with, it proved to be significant in reference to free radical scavenging action. The monoamine oxidase A bio-analysis was also executed to recognize viable anti-depressive actions manifesting that extracts with water and methanol retarded the enzyme, in its turn, it perform pivotal action in transport of neuron metabolic products. Although, analysis show that GABA and acetylhydrolyase have no biological action. Generally, the methanolic extract with methanol proved to be efficacious than compared with extract of water (López *et al.,* 2009).

Tinospora Cordifolia (Thunb.) Miers. (Menispermaceae)

T. cordifolia is characterized as a hairless, impermanent and creeping plant. It is native to torridzone of India and originally consumed as a powder, stem extract of *T. cordifolia* with starch otherwise known as satwa, and concoction. The roots of plant are highly resistive to strain, leprosy and malaria (Nayampalli *et al.,* 1982; Zhao *et al.,* 1991). *T. cordifolia* are mainly stuffed with underlying ingredients viz. glycosides, phenolics, diterpenoid lactones, sesquiterpenoid, polysaccharides, alkaloids and aliphatic compounds (Singh *et al.,* 2003). *T. cordifolia* is well-known

to contain plentiful mean of trace elements viz. Cu and Zn playing a crucial role of anti-oxidizing agent and provide shielded effects to cells from any harm i.e. ill impacts of oxygen radical (Zinc and Copper) which act as antioxidants and protects cells from the damaging effects of oxygen radicals owing to actuation of defense system (Chulet & Pradhan, 2009). *T. cordifolia* is thought to contain improving potency of learning and remembrance (Agarwal *et al.,* 2002).

Benincasa Hispida (Thunb.) Cogn. (Cucurbitaceae)

It is a creeping herb and highly grown in the form of vegetables in the meadows of India. The fruit of *B. hispida* is chiefly cylindrical in shape with coverage of waxen floweret (Sharma, 1999). Very important phyto-nutrients such as flavonoids, steroids, saponins and alkaloids are found in *B. hispida* (Battu et al., 2007). *B. cerifera* functions as a reactive oxygen species of scavenger and is seriously resistive to oxidizing agent (Bhalodia *et al.,* 2009). The plant plays a role in tissue protection via antioxidant action followed by inhibitory action on colchicine that persuade Alzheimer's disorder (Lim, 2007). *B. hispida* has importance with regard to its medicinal value and used in treatment of anxiety neurosis (Yogita & Chandola, 2005).

Acorus Calamus Linn. (Acoraceae)

A. calamus an evergreen, partially aquatic, aromatic herb having circular rootstalk with little bit upright and flat and grass like pointed leaves. It is native to India. Rhizome is beneficial organ of plant with characteristics of Medhya drug. Four century ago, traditional medicines of China and India have been used to manage many disorders related to central nervous system (Lai *et al.,* 2002; Mukherjee *et al.,* 2007). Very energetic elements present in *A. calamus* are elemicine, α-asarone, cis-isoelemicine, camphene, geometric isomerisms of isoeugenol and their methyl ethers, P-cymene, bgurjunene, a-selinene, camphor,terpinen-4-ol, b-cadinene, a-calacorene and aterpineol acorone, coragermacrone, 2-deca–4,7 dienol, acrenone, preisocalamendiol and linalool.coradin, calamendiol, galangin, 2, 4, 5- trimethoxy benzaldehyde, pathulenol, 2,5- dimethoxybenzoquinone and sitosterol (Mazza, 1985; Williamson *et al.,*1988). It has also been used to arrest pain and convulsions (Jayaraman *et al.,* 2010). The plant proved to be helpful in specific diagnosis of schizophrenic and improved clarity of speech in children (Fozdar *et al.,*1962).

CONCLUSION

Neurodegenerative diseases and other associated disorders are very common in today's modern world. The neurodegenerative disorders include diseases like Parkinson's disease Huntington's disease, amnesia, Alzheimer's disease etc. Synthetic drugs are available for the treatment of these disease. However, these drugs are least effective and are unable to provide permanent solution for the problem other than this they also possess severe side effects. Different phytochemicals obtained from variety of different plants have garnered significant attention by proving helpful in the mitigation of these diseases. The above chapter highlights some of the important plants which possess different cognitive enhancement abilities in the light of their pharmacological and ethno-botanical characteristics.

REFERENCES

Agarwal, A., Malini, S., Bairy, K. L., & Rao, M. S. (2002). Effect of *Tinospora cardifolia* on learning and memory in normal and memory deficit rats. *Indian Journal of Pharmacology*, *34*(5), 339–349.

Anekonda, T. S., & Reddy, P. H. (2005). Can herbs provide a new generation of drugs for treating Alzheimer's disease? *Brain Research. Brain Research Reviews*, *50*(2), 361–376. doi:10.1016/j.brainresrev.2005.09.001 PMID:16263176

Ansari, N., & Khodagholi, F. (2013). Natural products as promising drug candidates for the treatment of Alzheimer's disease: Molecular mechanism aspect. *Current Neuropharmacology*, *11*(4), 414–429. doi:10.2174/1570159X11311040005 PMID:24381531

Ansari, N., Khodagholi, F., & Amini, M. (2011). 2-Ethoxy-4, 5-diphenyl-1, 3-oxazine-6-one activates the Nrf2/HO-1 axis and protects against oxidative stress-induced neuronal death. *European Journal of Pharmacology*, *658*(2-3), 84–90. doi:10.1016/j.ejphar.2011.02.028 PMID:21371450

Ashabi, G., Ramin, M., Azizi, P., Taslimi, Z., Alamdary, S. Z., Haghparast, A., & Khodagholi, F. (2012). ERK and p38 inhibitors attenuate memory deficits and increase CREB phosphorylation and PGC-1α levels in Aβ-injected rats. *Behavioural Brain Research*, *232*(1), 165–173. doi:10.1016/j.bbr.2012.04.006 PMID:22510382

Battu, G. R., Mamidipalli, S. N., Parimi, R., Viriyala, R. K., Patchula, R. P., & Mood, L. R. (2007). Hypoglycemic and anti-hyperglycemic effect of alcoholic extract of *Benincasa hispida* in normal and in alloxan induced diabetic rats. *Pharmacognosy Magazine*, *3*(10), 101.

Benishin, C. G. (1992). Actions of ginsenoside Rb1 on choline uptake in central cholinergic nerve endings. *Neurochemistry International*, *21*(1), 1–5. doi:10.1016/0197-0186(92)90061-U PMID:1338897

Bhalodia, Y. S., Patel, N. J., Patel, R. K., Vaghasiya, J. D., Jivani, N. P., & Sheth, N. R. (2009). *Benincasa cerifera* ameliorates renal ischemia/reperfusion injury in hyperlipidemic rat. *Pharmacognosy Research*, *1*(6), 406.

Birari, R., Javia, V., & Bhutani, K. K. (2010). Antiobesity and lipid lowering effects of *Murraya koenigii* (L.) Spreng leaves extracts and mahanimbine on high fat diet induced obese rats. *Fitoterapia*, *81*(8), 1129–1133. doi:10.1016/j.fitote.2010.07.013 PMID:20655993

Birks, J., & Evans, J. G. (2009). *Ginkgo biloba* for cognitive impairment and dementia. *Cochrane Database of Systematic Reviews*, 1. doi:10.1002/14651858.CD003120.pub3 PMID:19160216

Blumenthal, M., Goldberg, A., & Brinckmann, J. (2000). *Herbal Medicine. Expanded Commission E monographs*. Integrative Medicine Communications.

Bores, G. M., Huger, F. P., Petko, W., Mutlib, A. E., Camacho, F., Rush, D. K., & Davis, L. (1996). Pharmacological evaluation of novel Alzheimer's disease therapeutics: Acetylcholinesterase inhibitors related to galanthamine. *The Journal of Pharmacology and Experimental Therapeutics*, *277*(2), 728–738. PMID:8627552

Bradwejn, J., Zhou, Y., Koszycki, D., & Shlik, J. (2000). A double-blind, placebo-controlled study on the effects of Gotu Kola (*Centella asiatica*) on acoustic startle response in healthy subjects. *Journal of Clinical Psychopharmacology*, *20*(6), 680–684. doi:10.1097/00004714-200012000-00015 PMID:11106141

Chen, W. W., Zhang, X. I. A., & Huang, W. J. (2016). Role of neuroinflammation in neurodegenerative diseases. *Molecular Medicine Reports*, *13*(4), 3391–3396. doi:10.3892/mmr.2016.4948 PMID:26935478

Chen, X., & Pan, W. (2014). The treatment strategies for neurodegenerative diseases by integrative medicine. *Integrative Medicine International*, *1*(4), 223–225. doi:10.1159/000381546

Choi, B.-M., Kim, H.-J., Oh, G.-S., Pae, H.-O., Oh, H., Jeong, S., & Chung, H.-T. (2002). 1, 2, 3, 4, 6-Penta-O-galloyl-beta-D-glucose protects rat neuronal cells (Neuro 2A) from hydrogen peroxide-mediated cell death via the induction of heme oxygenase-1. *Neuroscience Letters*, *328*(2), 185–189. doi:10.1016/S0304-3940(02)00513-X PMID:12133584

Chou, C.-H., Gong, C.-L., Chao, C.-C., Lin, C.-H., Kwan, C.-Y., Hsieh, C.-L., & Leung, Y.-M. (2009). Rhynchophylline from *Uncaria rhynchophylla* functionally turns delayed rectifiers into A-Type K+ channels. *Journal of Natural Products*, *72*(5), 830–834. doi:10.1021/np800729q PMID:19331340

Chulet, R., & Pradhan, P. (2009). A review on rasayana. *Pharmacognosy Reviews*, *3*(6), 229.

Chung, I.-W., Moore, N. A., Oh, W.-K., O'Neill, M. F., Ahn, J.-S., Park, J.-B., ... Kim, Y. S. (2002). Behavioural pharmacology of polygalasaponins indicates potential antipsychotic efficacy. *Pharmacology, Biochemistry, and Behavior*, *71*(1-2), 191–195. doi:10.1016/S0091-3057(01)00648-7 PMID:11812522

Crane, P. K., & Doody, R. S. (2009). Donepezil treatment of patients with MCI: A 48-week randomized, placebo-controlled trial. *Neurology*, *73*(18), 1514–1516. doi:10.1212/WNL.0b013e3181bd6c25 PMID:19884584

Desai, A. K., & Grossberg, G. T. (2005). Diagnosis and treatment of Alzheimer's disease. *Neurology*, *64*(12suppl 3), 34–39. doi:10.1212/WNL.64.12_suppl_3.S34 PMID:15994222

Dhanasekaran, M., Holcomb, L. A., Hitt, A. R., Tharakan, B., Porter, J. W., Young, K. A., & Manyam, B. V. (2009). *Centella asiatica* extract selectively decreases amyloid β levels in hippocampus of Alzheimer's disease animal model. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *23*(1), 14–19. doi:10.1002/ptr.2405 PMID:19048607

Drever, B. D., Anderson, W. G. L., Riedel, G., Kim, D. H., Ryu, J. H., Choi, D.-Y., & Platt, B. (2008). The seed extract of *Cassia obtusifolia* offers neuroprotection to mouse hippocampal cultures. *Journal of Pharmacological Sciences*, *107*(4), 380–392. doi:10.1254/jphs.08034FP PMID:18719316

Elmore, S. (2007). Apoptosis: A review of programmed cell death. *Toxicologic Pathology*, *35*(4), 495–516. doi:10.1080/01926230701320337 PMID:17562483

Fozdar, N. G., Bauadia, V. N., & Vahia, N. S. (1962). Preliminary Report Of An Indigenous Drug" *Acorus calamus*" In Psychiatric Disorders. *Indian Journal of Psychiatry*, *4*(1), 12.

Freese, J. L., Pino, D., & Pleasure, S. J. (2010). Wnt signaling in development and disease. *Neurobiology of Disease*, *38*(2), 148–153. doi:10.1016/j.nbd.2009.09.003 PMID:19765659

Fujiwara, H., Iwasaki, K., Furukawa, K., Seki, T., He, M., Maruyama, M., & Saido, T. C. (2006). *Uncaria rhynchophylla*, a Chinese medicinal herb, has potent antiaggregation effects on Alzheimer's β-amyloid proteins. *Journal of Neuroscience Research*, *84*(2), 427–433. doi:10.1002/jnr.20891 PMID:16676329

Fujiwara, H., Tabuchi, M., Yamaguchi, T., Iwasaki, K., Furukawa, K., Sekiguchi, K., & Saido, T. C. (2009). A traditional medicinal herb *Paeonia suffruticosa* and its active constituent 1, 2, 3, 4, 6-penta-O-galloyl-β-d-glucopyranose have potent anti-aggregation effects on Alzheimer's amyloid β proteins in vitro and in vivo. *Journal of Neurochemistry*, *109*(6), 1648–1657. doi:10.1111/j.1471-4159.2009.06069.x PMID:19457098

Hirsch, E. C., & Hunot, S. (2009). Neuroinflammation in Parkinson's disease: A target for neuroprotection? *Lancet Neurology*, *8*(4), 382–397. doi:10.1016/S1474-4422(09)70062-6 PMID:19296921

Ho, Y.-S., Yu, M.-S., Yang, X.-F., So, K.-F., Yuen, W.-H., & Chang, R. C.-C. (2010). Neuroprotective effects of polysaccharides from wolfberry, the fruits of *Lycium barbarum*, against homocysteine-induced toxicity in rat cortical neurons. *Journal of Alzheimer's Disease*, *19*(3), 813–827. doi:10.3233/JAD-2010-1280 PMID:20157238

Hou, Y.-C., Chao, P.-D. L., & Chen, S.-Y. (2000). Honokiol and magnolol increased hippocampal acetylcholine release in freely-moving rats. *The American Journal of Chinese Medicine*, *28*(3-4), 379–384. doi:10.1142/S0192415X00000441 PMID:11154051

Houghton, P. J., & Howes, M.-J. (2005). Natural products and derivatives affecting neurotransmission relevant to Alzheimer's and Parkinson's disease. *Neuro-Signals*, *14*(1-2), 6–22. doi:10.1159/000085382 PMID:15956811

Howes, M. J. R., & Houghton, P. (2003). Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function. *Pharmacology, Biochemistry, and Behavior*, *75*(3), 513–527. doi:10.1016/S0091-3057(03)00128-X PMID:12895669

Hsieh, C.-L., Ho, T.-Y., Su, S.-Y., Lo, W.-Y., Liu, C.-H., & Tang, N.-Y. (2009). *Uncaria rhynchophylla* and rhynchophylline inhibit c-Jun N-terminal kinase phosphorylation and nuclear factor-κB activity in kainic acid-treated rats. *The American Journal of Chinese Medicine*, *37*(2), 351–360. doi:10.1142/S0192415X09006898 PMID:19507277

Huang, K. C. (1993). *Yan Hu Suo–the dried tuber of Corydalis turtschaninovii Bess f. yanhusu (Papaveraceae). The Pharmacology of Chinese Herbs*. Boca Raton, FL: CRC Press.

Huang, K. C. (1998). *The pharmacology of Chinese herbs*. Routledge.

Irwin, R. L., & Smith Iii, H. J. (1960). Cholinesterase inhibition by galanthamine and lycoramine. *Biochemical Pharmacology*, *3*(2), 147–148. doi:10.1016/0006-2952(60)90030-7 PMID:13853036

Jalsrai, A., Numakawa, T., Kunugi, H., Dieterich, D. C., & Becker, A. (2016). The neuroprotective effects and possible mechanism of action of a methanol extract from *Asparagus cochinchinensis: In vitro* and *in vivo* studies. *Neuroscience*, *322*, 452–463. doi:10.1016/j.neuroscience.2016.02.065 PMID:26947129

Jayaraman, R., Anitha, T., & Joshi, V. D. (2010). Analgesic and anticonvulsant effects of *Acorus calamus* roots in mice. *International Journal of Pharm Tech Research*, *2*(1), 552–555.

Joshi, H., & Parle, M. (2006). Antiamnesic effects of *Desmodium gangeticum* in mice. *Yakugaku Zasshi*, *126*(9), 795–804. doi:10.1248/yakushi.126.795 PMID:16946593

Kim, D. H., Hyun, S. K., Yoon, B. H., Seo, J.-H., Lee, K.-T., Cheong, J. H., & Ryu, J. H. (2009). Gluco-obtusifolin and its aglycon, obtusifolin, attenuate scopolamine-induced memory impairment. *Journal of Pharmacological Sciences*, *111*(2), 110–116. doi:10.1254/jphs.08286FP PMID:19834282

Kim, D. S. H. L., Park, S.-Y., & Kim, J.-Y. (2001). Curcuminoids from *Curcuma longa* L.(Zingiberaceae) that protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from βA (1–42) insult. *Neuroscience Letters*, *303*(1), 57–61. doi:10.1016/S0304-3940(01)01677-9 PMID:11297823

Kim, Y. C., Kim, S. R., Markelonis, G. J., & Oh, T. H. (1998). Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. J Neurosci Res 53: 426-432. *Journal of Neuroscience Research*, *54*(1), 123–123. doi:10.1002/(SICI)1097-4547(19981001)54:1<123::AID-JNR13>3.0.CO;2-8 PMID:9778146

Kleijnen, J., & Knipschild, P. (1992). *Ginkgo biloba* for cerebral insufficiency. *British Journal of Clinical Pharmacology*, *34*(4), 352–358. doi:10.1111/j.1365-2125.1992.tb05642.x PMID:1457269

Kuang, P., Tao, Y., & Tian, Y. (1996). Effect of radix Salviae miltiorrhizae on nitric oxide in cerebral ischemic-reperfusion injury. *Journal of Traditional Chinese Medicine= Chung i tsa chih ying wen pan, 16*(3), 224-227.

Kuang, P., Wu, W., Liu, J., Zhang, F., & Pu, C. (1991). The effect of radix Salviae Miltiorrhizae (RSM) on substance P in cerebral ischemia--animal experiment. *Journal of traditional Chinese medicine= Chung i tsa chih ying wen pan, 11*(2), 123-127.

Kuang, P., & Xiang, J. (1994). Effect of *Radix salviae* miltiorrhizae on EAA and IAA during cerebral ischemia in gerbils: a microdialysis study. *Journal of Traditional Chinese medicine= Chung i tsa chih ying wen pan, 14*(1), 45-50.

Kuang, P. G., Wu, W. P., Zhang, F. Y., Liu, J. X., & Pu, C. Q. (1989). The effect of radix Salviae miltiorrhizae on vasoactive intestinal peptide in cerebral ischemia: an animal experiment. *Journal of Traditional Chinese Medicine= Chung i tsa chih ying wen pan, 9*(3), 203-206.

Kulkarni, C., Pattanshetty, J. R., & Amruthraj, G. (1988). Effect of alcoholic extract of *Clitoria ternatea* Linn. on central nervous system in rodents. *Indian Journal of Experimental Biology*, *26*(12), 957–960. PMID:3254867

Lai, X. Y., Liang, H., & Zhao, Y. Y. (2002). A survey of the studies on chemical constituents and pharmacological activities of Acorus plants. *Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi=. Zhongguo Zhongyao Zazhi*, *27*(3), 161–165. PMID:12807142

Lee, J., Son, D., Lee, P., Kim, D. K., Shin, M. C., Jang, M. H., ... Kim, H. (2003). Protective effect of methanol extract of *Uncaria rhynchophylla* against excitotoxicity induced by N-methyl-D-aspartate in rat hippocampus. *Journal of Pharmacological Sciences*, *92*(1), 70–73. doi:10.1254/jphs.92.70 PMID:12832857

Li, C., Yang, J., Yu, S., Chen, N., Xue, W., Hu, J., & Zhang, D. (2008). Triterpenoid saponins with neuroprotective effects from the roots of *Polygala tenuifolia. Planta Medica*, *74*(02), 133–141. doi:10.1055-2008-1034296 PMID:18256974

Liao, B., Newmark, H., & Zhou, R. (2002). Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. *Experimental Neurology*, *173*(2), 224–234. doi:10.1006/exnr.2001.7841 PMID:11822886

Lim, S. J. (2007). Effects of fractions of *Benincasa hispida* on antioxidative status in streptozotocin induced diabetic rats. *Journal of Nutrition and Health*, *40*(4), 295–302. doi:10.4163/jnh.2018.51.4.295

Liu, P., Hu, Y., Guo, D.-H., Lu, B.-R., Rahman, K., Mu, L.-H., & Wang, D.-X. (2010). Antioxidant activity of oligosaccharide ester extracted from *Polygala tenuifolia* roots in senescence-accelerated mice. *Pharmaceutical Biology*, *48*(7), 828–833. doi:10.3109/13880200903283707 PMID:20645784

López, V., Martín, S., Gómez-Serranillos, M. P., Carretero, M. E., Jäger, A. K., & Calvo, M. I. (2009). Neuroprotective and neurological properties of *Melissa officinalis. Neurochemical Research*, *34*(11), 1955–1961. doi:10.100711064-009-9981-0 PMID:19760174

Luo, L., Wang, J. N., Kong, L. D., Jiang, Q. G., & Tan, R. X. (2000). Antidepressant effects of Banxia Houpu decoction, a traditional Chinese medicinal empirical formula. *Journal of Ethnopharmacology*, *73*(1-2), 277–281. doi:10.1016/S0378-8741(00)00242-7 PMID:11025166

Mazza, G. (1985). Gas chromatographic and mass spectrometric studies of the constituents of the rhizome of calamus: I. The volatile constituents of the essential oil. *Journal of Chromatography. A*, *328*, 179–194. doi:10.1016/S0021-9673(01)87389-1

Mizumaki, Y., Kurimoto, M., Hirashima, Y., Nishijima, M., Kamiyama, H., Nagai, S., & Endo, S. (2002). Lipophilic fraction of *Panax ginseng* induces neuronal differentiation of PC12 cells and promotes neuronal survival of rat cortical neurons by protein kinase C dependent manner. *Brain Research*, *950*(1-2), 254–260. doi:10.1016/S0006-8993(02)03049-4 PMID:12231251

Mizuno, Y. (2014). Recent research progress in and future perspective on treatment of Parkinson's disease. *Integrative Medicine International*, *1*(2), 67–79. doi:10.1159/000365571

Moncada, S. (1991). Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacological Reviews*, *43*, 109–142. PMID:1852778

Mudgal, V. (1975). Studies on medicinal properties of *Convolvulus pluricaulis* and *Boerhaavia diffusa. Planta Medica*, *28*(05), 62–68. doi:10.1055-0028-1097830 PMID:1178789

Mukherjee, P. K., Kumar, V., Mal, M., & Houghton, P. J. (2007). *In vitro* acetylcholinesterase inhibitory activity of the essential oil from *Acorus calamus* and its main constituents. *Planta Medica*, *73*(03), 283–285. doi:10.1055-2007-967114 PMID:17286241

Nahata, A., Patil, U. K., & Dixit, V. K. (2008). Effect of *Convulvulus pluricaulis* Choisy. on learning behaviour and memory enhancement activity in rodents. *Natural Product Research*, *22*(16), 1472–1482. doi:10.1080/14786410802214199 PMID:19023811

Nahata, A., Patil, U. K., & Dixit, V. K. (2010). Effect of *Evolvulus alsinoides* Linn. on learning behavior and memory enhancement activity in rodents. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *24*(4), 486–493. PMID:19610035

Naito, R., & Tohda, C. (2006). Characterization of anti-neurodegenerative effects of *Polygala tenuifolia* in Aβ (25-35)-treated cortical neurons. *Biological & Pharmaceutical Bulletin*, *29*(9), 1892–1896. doi:10.1248/bpb.29.1892 PMID:16946504

Nayampalli, S., Ainapure, S. S., & Nadkarni, P. M. (1982). Study of antiallergic acid bronchodilator effects of *Tinospora cordifolia. The Indian Journal of Pharmacy*, *14*, 64–66.

Nishiyama, N., Chu, P., & Saito, H. (1995). Beneficial effects of biota, a traditional Chinese herbal medicine, on learning impairment induced by basal forebrain-lesion in mice. *Biological & Pharmaceutical Bulletin*, *18*(11), 1513–1517. doi:10.1248/bpb.18.1513 PMID:8593469

Nishiyama, N., Zhou, Y., & Saito, H. (1994). Ameliorative effects of chronic treatment using DX-9386, a traditional Chinese prescription, on learning performance and lipid peroxide content in senescence accelerated mouse. *Biological & Pharmaceutical Bulletin*, *17*(11), 1481–1484. doi:10.1248/bpb.17.1481 PMID:7703968

Pak, M. E., Kim, Y. R., Kim, H. N., Ahn, S. M., Shin, H. K., Baek, J. U., & Choi, B. T. (2016). Studies on medicinal herbs for cognitive enhancement based on the text mining of Dongeuibogam and preliminary evaluation of its effects. *Journal of Ethnopharmacology*, *179*, 383–390. doi:10.1016/j.jep.2016.01.006 PMID:26773844

Park, C. H., Choi, S. H., Koo, J. W., Seo, J. H., Kim, H. S., Jeong, S. J., & Suh, Y. H. (2002). Novel cognitive improving and neuroprotective activities of *Polygala tenuifolia* Willdenow extract, BT-11. *Journal of Neuroscience Research*, *70*(3), 484–492. doi:10.1002/jnr.10429 PMID:12391609

Pearson, V. E. (2001). Galantamine: A new Alzheimer drug with a past life. *The Annals of Pharmacotherapy*, *35*(11), 1406–1413. doi:10.1345/aph.1A092 PMID:11724094

Quigley, B. J. Jr, & Kowall, N. W. (1991). Substance P-like immunoreactive neurons are depleted in Alzheimer's disease cerebral cortex. *Neuroscience*, *41*(1), 41–60. doi:10.1016/0306-4522(91)90199-X PMID:1711654

Rahman, H., Shaik, H. A., Madhavi, P., & Eswaraiah, M. C. (2011). A review: Pharmacognostics and pharmacological profiles of *Nardastachys jatamansi* DC. *Elixir Pharmacy*, *39*, 5017–5020.

Rai, K. S., Murthy, K. D., Karanth, K. S., Nalini, K., Rao, M. S., & Srinivasan, K. K. (2002). *Clitoria ternatea* root extract enhances acetylcholine content in rat hippocampus. *Fitoterapia*, *73*(7-8), 685–689. doi:10.1016/S0367-326X(02)00249-6 PMID:12490229

Rajakrishnan, V., Viswanathan, P., Rajasekharan, K. N., & Menon, V. P. (1999). Neuroprotective role of curcumin from *Curcuma longa* on ethanol-induced brain damage. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *13*(7), 571–574. doi:10.1002/(SICI)1099-1573(199911)13:7<571::AID-PTR494>3.0.CO;2-7 PMID:10548748

Russo, A., & Borrelli, F. (2005). Bacopa monniera, a reputed nootropic plant: An overview. *Phytomedicine*, *12*(4), 305–317. doi:10.1016/j.phymed.2003.12.008 PMID:15898709

Sharma, P. V. (1999). *Dravyaguna Vijnana* (Vol. 2). Varanasi: Chaukhambha Bharti Academy.

Shi, J.-S., Yu, J.-X., Chen, X.-P., & Xu, R.-X. (2003). Pharmacological actions of *Uncaria* alkaloids, rhynchophylline and isorhynchophylline. *Acta Pharmacologica Sinica*, *24*(2), 97–101. PMID:12546715

Singh, S. S., Pandey, S. C., Srivastava, S., Gupta, V. S., Patro, B., & Ghosh, A. C. (2003). Chemistry and medicinal properties of *Tinospora cordifolia* (Guduchi). *Indian Journal of Pharmacology*, *35*(2), 83–91.

Squires, R. F., Ai, J., Witt, M.-R., Kahnberg, P., Saederup, E., Sterner, O., & Nielsen, M. (1999). Honokiol and magnolol increase the number of [3 H] muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites. *Neurochemical Research*, *24*(12), 1593–1602. doi:10.1023/A:1021116502548 PMID:10591411

Sultana, R., & Butterfield, D. A. (2010). Role of oxidative stress in the progression of Alzheimer's disease. *Journal of Alzheimer's Disease*, *19*(1), 341–353. doi:10.3233/JAD-2010-1222 PMID:20061649

Tang, W., & Eisenbrand, G. (2013). *Chinese drugs of plant origin: chemistry, pharmacology, and use in traditional and modern medicine*. Springer Science & Business Media.

Taranalli, A. D., & Cheeramkuzhy, T. C. (2000). Influence of Clitoria ternatea extracts on memory and central cholinergic activity in rats. *Pharmaceutical Biology*, *38*(1), 51–56. doi:10.1076/1388-0209(200001)3811-BFT051 PMID:21214440

Tejada, S., Setzer, N., Daglia, M., Nabavi, S. F., Sureda, A., Braidy, N., ... Nabavi, S. M. (2017). Neuroprotective effects of Ellagitannins: A brief review. *Current Drug Targets*, *18*(13), 1518–1528. doi:10.2174/1389450117666161005112002 PMID:27719661

Umeyama, A., Yahisa, Y., Okada, M., Okayama, E., Uda, A., Shoji, N., & Hashimoto, T. (2010). Triterpene esters from Uncaria rhynchophylla drive potent IL-12-dependent Th1 polarization. *Journal of Natural Medicines*, *64*(4), 506–509. doi:10.100711418-010-0438-1 PMID:20585989

Vasudevan, M., & Parle, M. (2009). Antiamnesic potential of *Murraya koenigii* leaves. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *23*(3), 308–316. doi:10.1002/ptr.2620 PMID:18844259

Veerendra Kumar, M. H., & Gupta, Y. K. (2003). Effect of *Centella asiatica* on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. *Clinical and Experimental Pharmacology & Physiology*, *30*(5-6), 336–342. doi:10.1046/j.1440-1681.2003.03842.x PMID:12859423

Vinutha, J. P. (2007). Acetyl cholinesterase inhibitory activity of methanolic and successive water extracts of *Nardostachys jatamansi. International Journal of Pharmacology*, *23*, 127–131.

Watanabe, C. M. H., Wolffram, S., Ader, P., Rimbach, G., Packer, L., Maguire, J. J., & Gohil, K. (2001). The *in vivo* neuromodulatory effects of the herbal medicine *Ginkgo biloba. Proceedings of the National Academy of Sciences of the United States of America*, *98*(12), 6577–6580. doi:10.1073/pnas.111126298 PMID:11381109

Wilkinson, D., & Murray, J. i. (2001). Galantamine: A randomized, double-blind, dose comparison in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *16*(9), 852–857. doi:10.1002/gps.409 PMID:11571763

Williamson, E. M. (2002). *Major herbs of Ayurveda*. Churchill Livingstone.

Williamson, E. M., Evans, F. J., & Wren, R. C. (1988). Potter's new cyclopedia of botanical drugs and preparations. Walden, UK: Saffron Walden.

Xu, Y., Cao, Z., Khan, I., & Luo, Y. (2008). Gotu Kola (*Centella asiatica*) extract enhances phosphorylation of cyclic AMP response element binding protein in neuroblastoma cells expressing amyloid beta peptide. *Journal of Alzheimer's Disease*, *13*(3), 341–349. doi:10.3233/JAD-2008-13311 PMID:18431001

Xue, W., Hu, J. F., Yuan, Y. H., Sun, J. D., Li, B. Y., Zhang, D. M., & Chen, N. H. (2009). Polygalasaponin XXXII from *Polygala tenuifolia* root improves hippocampal-dependent learning and memory. *Acta Pharmacologica Sinica*, *30*(9), 1211–1219. doi:10.1038/aps.2009.112 PMID:19684611

Yogita, A., & Chandola, H. M. (2005). *Clinico-experimental study of Kushmandadi Ghrita in Generalized Anxiety Disorder (DSM-IV) wsr to Chittodvega* (Thesis). IPGT and RA, GAU, Jamnagar, Gujarat.

Yu, M.-S., Leung, S. K.-Y., Lai, S.-W., Che, C.-M., Zee, S.-Y., So, K.-F., & Chang, R. C.-C. (2005). Neuroprotective effects of anti-aging oriental medicine *Lycium barbarum* against β-amyloid peptide neurotoxicity. *Experimental Gerontology*, *40*(8-9), 716–727. doi:10.1016/j.exger.2005.06.010 PMID:16139464

Yu, Z. F., Kong, L. D., & Chen, Y. (2002). Antidepressant activity of aqueous extracts of *Curcuma longa* in mice. *Journal of Ethnopharmacology*, *83*(1-2), 161–165. doi:10.1016/S0378-8741(02)00211-8 PMID:12413724

Yuen, M. F., Tam, S., Fung, J., Wong, D. H., Wong, B. Y., & Lai, C. L. (2006). Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: A 1-year prospective study. *Alimentary Pharmacology & Therapeutics*, *24*(8), 1179–1186. doi:10.1111/j.1365-2036.2006.03111.x PMID:17014576

Zhao, T., Wang, X., Rimando, A. M., & Che, C. (1991). Folkloric medicinal plants: *Tinospora sagittata* var. cravaniana and *Mahonia bealei. Planta Medica*, *57*(05), 505–505. doi:10.1055-2006-960188 PMID:1798808

Section 2
Role of Medicinal Plants in Microbial Diseases

Chapter 8
Anti-Malarial Drug Resistance: Need for Novel Natural Products

Manish Kumar Dwivedi
Indira Gandhi National Tribal University Amarkantak, India

Prashant Kumar Singh
https://orcid.org/0000-0002-8117-4592
Indira Gandhi National Tribal University Amarkantak, India

ABSTRACT

Malaria is a life-threatening infectious disease caused by a protozoan parasite of the genus Plasmodium. It is transmitted through the bites of infected female Anopheles mosquitoes. The global burden is estimated to be around 219 million cases in 87 countries. Natural compounds have been used primarily in the traditional medicine for thousands of years. For the treatment of malaria, natural products were used until the development of synthetic drugs, and most of the currently available anti-malarial drugs have been derived based on the compounds from these traditional medicinal plants. The current chapter tries to briefly indicate the emerging resistance against anti-malarial drugs and to discuss the recent research on natural products that have been evaluated for anti-malarial activity. Rigorous evaluation of the efficacy and safety of traditional medicines is required along with identification of active constituents in order to develop new drugs with novel mechanisms of action.

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INTRODUCTION

Traditional medicinal systems include various medicinal approaches and practices found at a particular region of the world and were the only system used for treating different types of diseases. These systems can be classified into various categories like Ayurveda, Siddha, Unani, Korean medicine, African medicine system, Irani system and traditional Chinese medicine (Lemonnier *et al.,* 2017). All these systems widely use medicinal plants in different combinations or formulations. In India, traditional systems are still being followed in many regions for treating different ailments. It is eminent that natural products have remained a high productive source for drug discovery and development process. Due to lack of modern medicines and medical facilities there is strong belief in the use of traditional medicinal system that relies upon the experience gained over thousands of years in diverse regions of the world (Deepak, 2008). Today, researchers have started to bank upon this vast array of knowledge for the development of modern drugs and have isolated various bioactive compounds including alkaloids, flavonoids, tannins, phenolics, amines, terpenoids, proteins, etc. that have been reported and used for curing various diseases.

Tropical and subtropical neglected infectious diseases such as leishmaniasis, dengue, leprosy, trachoma, lymphatic filariasis, malaria and tuberculosis affect almost one-sixth part of the world's population that resides mainly in non-developed countries. Malaria is one of the infectious diseases, prevalent in countries with low income groups leading to millions of deaths annually. The patients affected with malaria and the public health systems cannot afford the financial return required by most pharmaceutical companies. This leads to minimal interest of pharmaceutical companies for investing in research and development for novel drug development against neglected diseases. Currently, most research is being undertaken primarily by government research and academic institutions.

The main objectives of the proposed chapter is to review the current status of the traditional medicinal system, the development of plant-based anti-malarial drugs, the structure and activity relationships of the pure compounds with antimalarial potential, current status of the active molecules and future prospects of the natural products in antimalarial drug discovery programs.

HERBAL MEDICINE

Natural products are a large assemblage of diverse secondary metabolites with widespread biological activities and are usually obtained from plants, marine animals and microorganisms. These compounds are widely used as medicines, flavoring

agents, or recreational drugs. Naturally these secondary metabolites are produced for self-defense, protection, competition, and species interactions (Demain, 2014).

Since prehistoric times, mankind is using medicinal plants for basic preventive and therapeutic health care. This form of knowledge known as "the traditional system of medicine" contains information about a large reservoir of herbal formulations and medicinal plants. Principles developed over the life time in different cultures are used in prophylactic, diagnostic or therapeutic purposes (Sen & Chakroborty, 2015). As per World Health Organization (WHO), around 80% of the global population depends on traditional medicine or drugs obtained from the natural world (WHO, 2002). Adverse effects can be observed if traditional medicines or practices are followed improperly as minor changes in the concentration of metabolites can lead to altered activities (Sen & Chakroborty, 2015). Modern healthcare system finds its roots in the plant based medicines. In countries like United States, one of the four allopathic prescriptions are either purified from plants or synthesized based on plant molecules (Mazid *et al.,* 2012). With the increasing population, allopathic medicines are out of reach from a large section of the communities living in rural and remote areas of the country due to high prices and their side effects. These parameters have led to the increase in popularity of alternative medicines especially among rural, tribal and remote populations.

Malaria is the second most common infectious disease across the world caused by protozoan parasite *Plasmodium* sp., and spread by infected female *Anopheles* mosquitoes. Five different species of *Plasmodium* parasites i.e. *Plasmodium falciparum*, *P. malariae*, *P. vivax, P. ovale* and *P. knowlesi* are known to infect humans amongst them *P. falciparum and P. vivax* are the most common species that infects humans. The major vectors of human malarial parasites are *Anopheles gambiae, A. funestus, A. arabiensis, A. melas, A. arabiensis*, *A. Stephensi, A. fleviatilis* and *A. culicifacies.*

Once the plasmodium parasite enters the body, they infect the liver and matures. Mature parasites leave the hepatocytes to infect the red blood cells (RBC). In RBC, the parasites multiply bursting the infected RBC within 48 to 72 h. Symptoms of malaria are visible within 10 days to 4 weeks after the bite of the infected mosquito in non-immune persons but in people with strong immunity, the symptoms may not develop for several months. Common symptoms of malaria include high fever, headache, vomiting, muscular pain, nausea, chills, abdominal pain and sweating. Children and pregnant women often develop anemia, cerebral anemia, and metabolic acidosis, etc.

Malaria is endemic in almost 100 countries, mostly located in poor tropical Asia, Africa and Latin American regions (WHO, 2014). In 2017 around 80% of malaria deaths were reported from the 17 countries in the WHO African Region and India. Nigeria (19%), Democratic Republic of the Congo (11%), Burkina Faso (6%),

United Republic of Tanzania (5%), Sierra Leone (4%), Niger (4%) and India (4%) were the major seven countries that accounted for 53% of the total deaths reported. India is the only country among the nations with maximum disease burden (about 9.5 million) that has managed to reduce its disease burden (24% reduction) between 2016 and 2017 (WHO, 2018). The RTS, S also known as Mosquirix is the world's first malaria vaccine consisting of hepatitis B surface antigen virus like particles. The vaccine incorporates a segment *P. falciparum* circum sporozoite protein. The vaccine is partially effective against malaria parasite *P. falciparum* in young children and infants. The vaccine functions by triggering the immune system and prevents the parasites infection, maturation and multiplication in the liver thereby inhibiting the reinfection of the red blood cells (Nielsen *et al.*, 2018). Young children will be immunized through national immunization programs in parts of three sub-Saharan African countries namely Ghana, Kenya, and Malawi starting from 2019 (Pringle *et al*., 2018).

Currently available antimalarial drugs are used in the form of prophylactic treatment or for the treatment of an acute attack of the disease and belong to three broad groups namely, the aryl-amino alcohol compounds (chloroquine, lumefantrine, amodiaquine, mefloquine, quinine, primaquine, halofantrine), artemisinin derivatives (artemisinin, dihydroartemisinin, arteether, artesunate) and the the antifolates (proguanil, trimethoprim, pyrimethamine). The most widely used medicines in the fight against malaria are chloroquine, mefloquine and primaquine. The first line of drug to treat severe malaria is Quinine that is being used in India and many other countries around the world (Parija & Praharaj, 2011). Artemisinin derivatives such as arteether and artesunate are effective anti-malarial agents that display the fastest therapeutic response amongst all available anti-malarials leading to rapid parasitic clearance (White, 2009). Even after 400 years of usage Quinine still remains an important anti-malarial drug for treating malaria. All these antimalarial drugs were discovered and isolated from medicinal plants and are being chemically synthesized in large quantities.

NEED FOR PLANT-BASED ANTIMALARIAL DRUGS

Resistance against anti-malarial drugs has emerged as major global challenge against malaria control. The WHO defined anti-malarial drug resistance as "the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject." Drug resistance occurs through spontaneous mutation reducing sensitivity to a particular class of drugs including derivatives of artemisinin in *P. falciparum*, the dominant type of species of malaria. For some

drugs, only single point mutation occurs while for some multiple mutations are required for resistance emergence (Bruce-Chwatt *et al.*, 1986). Treatment regimens for *P. falciparum* and *P. vivax* are different with frequent resistance to older drugs. Resistance has been reported against all classes of anti-malarial drugs only with an exception of artemisinin and its derivatives (Achan *et al.*, 2011).

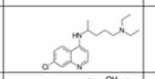
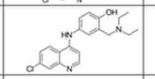
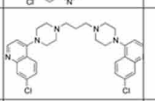
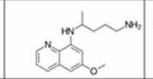
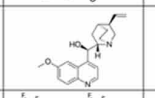
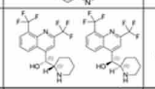
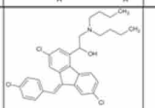
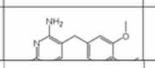
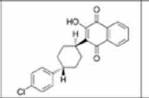
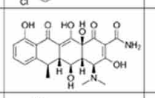
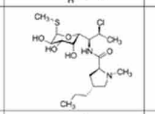
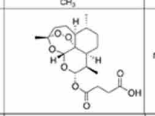
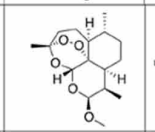
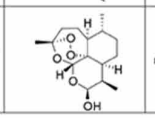
In the current chapter the historical emergence of anti-malarial drug resistance is being discussed. The biochemical mechanisms responsible for resistance have also been described for important anti-malarial drugs such artemisinin family drugs, chloroquine, antifolate, atovaquone, and quinine.

Resistance to Chloroquine

Chloroquine, a type of class-4-aminoquinoline is a generic drug used to treat malaria and was first time introduced in 1934 by Hans Andersag, during World War II. Chloroquine is a prototypical anti-malarial drug and is also effective against rheumatoid arthritis, liver abscesses, lupus erythematous and inflammation. Chloroquine have derivative such as chloroquinedi phosphate, chloroquine sulfate, chloroquinedi hydrochloride and chloroquine phosphate. The mechanism of action of chloroquine is not well defined but like quinine possesses plasmodicidal activity. Chloroquine is able to degrade parasite hemoglobin by inhibition of heme polymerase activity which is carried out in food vacuole of the parasite cell. Malarial parasites bio-crystallizes heme to form hemozoin, a non-toxic molecule. Chloroquine, in this system becomes protonated and provides an acidic pH system (4.7). Chloroquine functions by binding to the heme or protoporphyrin forming a complex that causes cell lysis due to high toxicity. The parasites are finally auto-digested by the cells of the immune system.

In late 1950s drug resistance against chloroquine was observed in Southeast Asia and South America, and spread widely in Africa from the 1970s to the 1980s. The chloroquine resistance in *P. falciparum* has spread to almost all the countries in the world till date (Baird, 2009). Chloroquine resistant parasites accumulate chloroquine in very low quantities, suggesting that the resistance results due to the non-availability of the drug at action site and not due to modifications of the chloroquine target site. It has been reported that there is an increase of 40-50 times chloroquine efflux in resistant parasites as compared to the sensitive parasites (Krogstad *et al.*, 1987). Interfering with the chloroquine flow system can reverse the mechanism by the use of resistance drugs (Martin & Oduola, 1987). At molecular level chloroquine resistance in *P. falciparum* has been reported due to a mutation at position 76 in the parasite PfCRT gene encoding a transporter molecule in the parasite vacuole (White, 2004). The point mutation in the PfCRT gene leads to higher expulsion rates of chloroquine in resistant parasites as compared to sensitive ones. Another gene

Table 1. List of drugs with reported resistance against malarial parasite

S. No	Drug class	Drug	Structure	Doses	Resistance	Country reported	Mechanism of action	Reference
1	4-Aminoquinoline	Chloroquine		25 mg base/kg	Since 1950	Southeast Asia and South America	Inhibition of hemozoin formation	(Baird JK, 2009; Krogstad DJ et al., 1987)
		Amodiaquine		-	Since 2002	Brazil, Papua New Guinea, Laos, Iran, Asia, East Africa, South America,	Like other quinoline derivatives, it is thought to inhibit heme polymerase activity.	(Baird JK, 2009; Krogstad DJ et al., 1987)
		Piperaquine		-	Since 2010	Southeast Asia, Western Cambodia	Inhibition of hemozoin formation	(Krogstad DJ et al., 1987; White NJ., 2004)
2	8-Aminoquinoline	Primaquine		30 mg should be given 14 days	-	Resistance in *P. vivax*	It may be acting by generating reactive oxygen species or by interfering with the electron transport in the parasite	(Krogstad DJ et al., 1987; White NJ., 2004)
		Quinine		100 mg	1910	Brazil, Southeast Asia	Inhibition of hemozoin, biocrystallization in Heme Detoxification pathway	(Krogstad DJ et al., 1987; White NJ., 2004)
3	Aryl-amino alcohol	Mefloquine		125 mg (1/2 tablet)/week	Since1980	Asia, Thai Cambodian Border	Acts as a blood schizonticide	(Baird JK, 2009; White NJ., 2004)
		Lumefantrine		-	No	-	Inhibits the formation of β-hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis	(Krogstad DJ et al., 1987; White NJ., 2004)
		Trimethoprim		-	Yes	-	Binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid (DHF)	(Cui, Mharakurwa, Ndiaye, Rathod, &
						Northeast states and Orissa. Resistance in *P. falciparum* to sulphadoxine/ pyrimethamine combination was first detected in Delhi in 1987	enzyme dihydropteroate synthetase	
5	Napthoquinone	Atovaquone		500-750 mg every 12 hours for 7 days	Since 1996, 2000	Thai Cambodian Border	Inhibition cytochrome	
		Doxycycline		-	No	-	Binding to ribosomal subunits and inhibiting protein synthesis	
6	Antibiotic	Clindamycin		-	-	-	Inhibition of protein synthesis and apicoplast	(Cui, Mharakurwa, Ndiaye, Rathod, & Rosenthal, 2015; White NJ., 2004)
		Artesunate		4 mg/kg/day/3days (Total 7 days)	Yes	-	Dihydroartemisinin (DHA) inhibition of calcium-dependent ATPase on endoplasmic membrane, which disrupts protein folding of parasites	(Cui, Mharakurwa, Ndiaye, Rathod, & Rosenthal, 2015; White NJ., 2004)
7	Artemisinin	Artemether		4 mg/kg/day/3days (Total 7 days)	Since 2001	Cambodia, Thailand border region of Southeast Asia	Free radical mechanism Heme alkylation	(Cui, Mharakurwa, Ndiaye, Rathod, & Rosenthal, 2015; White NJ., 2004)
		Dihydroartemisinin		2 mg/kg/day/6days	Since 2001	Cambodia, Thailand border region of Southeast Asia	Free radical mechanism Heme alkylation	(Cui, Mharakurwa, Ndiaye, Rathod, & Rosenthal, 2015; White NJ., 2004)

pfMDR1 with point mutation has also been associated with chloroquine resistant (Dorsey *et al.,* 2001).

Resistance to Artemisinin

Artemisinin is presently available most efficient anti-malarial drug capable for treating both *P. falciparum* and *P. vivax* infections. Artemisinin is isolated from *Artemisia annua* Linn. (Asteraceae), a common herb found in China and other places in the world. The anti-malarial activity of this plant was discovered by Tu You who was awarded with Nobel Prize (2015) for this achievement. Artemisinine is semi-synthetic drug which contains1, 2, 4-trioxane ring natural and a lactone peroxide that targets the erythrocytic stage of the parasite. Several artemisinine derivatives have been synthesized that includes artemether, artesunate, dihydroartimisinin, arteether etc. It has been shown that artemisinin interacts with intraparasitic heme to release toxic free radicals which in turn is selectivity lethal to the heme-iron rich parasite. Free radicals cause protein alkylation and damages parasites micro-organelles and membranes and also inhibit the P-type ATPase (PfATP6) of *P. falciparum.*

Although artemisinin resistance has gained worldwide attention, still artemisinins and its derivatives are an important component of the current malaria therapies. Initially the anti-malarial drug resistance was noted in Thailand, Cambodia and the border regions of Southeast Asia (Phyo *et al.*, 2012). Polymorphism in the *P. falciparum* multidrug resistance-1 (pfmdr1) gene that encodes the P-glycoprotein homolog has been linked to artemisinin resistance in *P. falciparum*. Modifications in the pfmdr1 gene sequence or copy number alters the transport of multiple drugs in or out of the parasite food vacuole and leads to decrease in sensitivity to the drug (Cui *et al*., 2012). Genome-wide association in field based studies had identified certain regions on chromosome 13 that have been associated with delayed parasitic clearance.

By the use of genomics approach mutations were identified in the propeller domain of *P. falciparum* kelch (K13) gene (PF3D7-1343700) that have been linked to the delayed parasite clearance after artemisinin therapy (Takala-Harrison *et al.,* 2013). Recently, using the molecular approaches it was observed that 39% of the 940 samples analyzed were positive for K13-propeller mutation (Tun *et al.*, 2015). In other reports from Cambodia, recrudescent infections have been reported after treatment with dihydroartemisinin/ piperaquine, raise the apprehension that artemisinin resistance is responsible for increase in resistance to artemisinin associated drugs.

Resistance to Quinine

Physicians have been treating fevers for thousands of years using herbal plants which were later replaced by different extracts, isolated pure compounds and finally synthetic drugs. Malaria was one of the primary diseases to be cured by such purified compound called quinine from the bark of *Cinchona officinalis* Linn. (Rubiaceae) in 1820. The cinchona trees were found in South America, and the bark was known as "fever bark" or "holy bark" due to isolation of quinine that was used for treating fever. The name quinine was given by French researchers "Joseph Caventou and Pierre Joseph Pelletier" in 1820. Initially quinine was naturally isolated from the bark of Cinchona tree and was being used to treat *P. falciparum* malaria. However, in 1944 American chemist W.E. Doering and R.B. Woodward used synthetic techniques to produce several derivatives of quinine. Quinine functions against the malaria parasite by acting against blood schizonts and gametocytes by inhibiting heme polymerase and gets concentrated in food vacuoles of *P. falciparum.* It is less effective and more toxic than chloroquine and is prescribed in chloroquine resistance cases.

Quinine is the oldest anti-malarial drug against which resistance was reported initially from Brazil and later from Southeast Asia (Da Silva & Benchimol, 2014). Resistance to quinine is linked with polymorphism within many transporters and the SNP has been linked to *pfmdr1, pfcrt* and *pfmrp1* gene expression patterns in quinine sensitivity. Additionally amplification of the *pfmdr1* gene has also been associated with quinine resistance. Several current studies have evaluated association between *in vitro* parasitic sensitivity, polymorphisms in a *pfnhe1* microsatellite and clinical outcomes against various drugs (Sinou *et al*., 2011). In some parasitic strains, *In vitro* efforts to down regulate the expression of pfnhe1 by ~50% has led to a 30% increase in quinine sensitivity (Nkrumah *et al.*, 2009).

Resistance to Atovaquone

In the 1980s atovaquone, a hydroxynaphthoquinone was developed by Welcome Laboratories as an antimalarial agent. It is a ubiquinone analogue approved by the FDA in fixed dose combination with proguanil (Malarone) for prophylaxis and therapeutic purposes in *P. falciparum* cases. Quick development of in vitro resistance and in initial clinical trials led to combination of atovaquone with proguanil. The efficacy of combination for the treatment of *P. falciparum* and *P. vivax* malaria has been documented by many studies.

Atovaquone at low nanomolar concentrations prevents in vitro *P. falciparum* development, it is even effective against multidrug resistant parasites. It also works as an anti-protozoal agent capable to treat pneumonia and babesiosis. Atovaquone is lipophilic in nature and highly protein bound and undergoes hepatic circulation.

The mechanism of action of atovaquone to kill the malaria parasites is still unknown; however it has been stipulated that severe disruption of mitochondrial physiology might be a probable cause of parasite death. It has been reported that the drug interferes by the mitochondria electron transporter proteins and also acts on ATP and pyrimidine biosynthesis specifically. It is thought to inhibit a mitochondrial enzyme dihydroorotate dehydrogenase, target the electron transport chain, cytochrome *bc1* complex damaging the membrane potential.

In the plasmodium species, drug resistance has been reported due to several different mechanisms, such as expression of specific drug targets, changes in drug permeability or changes in target enzyme (Garcia, 2010). Three proteins (cytochrome c oxidase subunits I and II, and cytochrome b are encoded by the tandemly arranged mitochondrial DNA in malaria parasites. Catalytic domains of cytochrome b have been proposed for the differential parasitic vulnerability to hydroxy naphtho quinones. Mutations in specific region of cytochrome b suggest a possible basis for altered response to anti-malarial drug hydroxynaphthoquinones. Recently it has been shown in atovaquone-resistant parasites that cytochrome b of the bc1 complex acts as the binding site for atovaquone (Wilson & Williamson, 1997).

It has been supported by experimental findings in *P. falciparum* that the mutation at the 268th place in site-b is linked to the unambiguously acquired resistance to atovaquone (Musset *et al.*, 2006). Emergence of drug resistance has been associated with monotherapy using atovaquone. Atovaquone resistance readily develops *in vitro* in *P. falciparum* cultures at low doses of the drug and has also been associated to the geographic region from which the parasites are obtained. Combination therapy including atovaquone and proguanil is very effective with no reports of recrudescence. It is evident that proguanil do not have any effect on electron transport or mitochondrial membrane potential alone but displays synergistic activity with atovaquone by lowering the atovaquone concentration at which is able to collapse the mitochondrial membrane electro-potential. The clinical trials involving the recommended combination of atovaquone and proguanil failed to report emergence of resistance against the combination. The probable mechanism of drug action and the emergence of resistance have been fairly understood before its market release, making the active post-release surveillance program much easier to monitor resistance emergence. There is much industrial hope from the combination of atovaquone and proguanil for prophylactic purposes (Syafruddin & Siregar, 1999).

Resistance to Antifolate

Antifolate agents are combination of two or more drugs (usually pyrimethamine and sulfadoxine) used for the treatment of malaria. Initially, pyrimethamine was in use individually but *P. vivax* and *P. falciparum* developed resistance in less than a year of

its use. The combination was effective against chloroquine-resistant uncomplicated malaria but there were reports of resistance from the South America and Asia Pacific regions (Hurwitz *et al.,* 1981).

Antifolate agents are sub-divided into Class I antifolates (inhibitors of dihydropteroate synthase) and Class II antifolates (inhibitors of dihydrofolate reductase). Point mutations in the genes coding for above mentioned target enzymes have been attributed the molecular cause for pyrimethamine and sulfa resistance (Imwong *et al.,* 2003). Sulfadoxine/ pyrimethamine combination was extensively used in 1990's in Africa for the treatment of chloroquine-resistant malaria till sulfadoxine/ pyrimethamine resistance emerged. Molecular epidemiology studies that utilized DNA microsatellite sequences suggested that pyrimethamine resistance transferred from Asia to Africa (Roper *et al.*, 2004).

In contradiction resistance to sulfa partners through *dhps* mutations is thought to arise by the de novo events in both Asia and sub-Saharan Africa (Alifrangis *et al*., 2014). Sulfadoxine/ pyrimethamine combination now been stopped as the first line treatment for *P. falciparum* infections. However, it is used as an ACT combination in most parts of India (Jain *et al.*, 2014), for protective therapy in pregnant women in Africa (Ter Kuile *et al.,* 2007), and in school children as chemopreventive agents for seasonal malaria in the Sub-Saharan Africa (Naidoo & Roper, 2013). It is also to be noted that sulfadoxine/ pyrimethamine resistance in *P. vivax* appeared in Asia and the Pacific Islands, where both *P. falciparum* and *P. vivax* coexist (Ganguly *et al.*, 2014).

There is an evolutionary race amongst the different species of the malaria parasites, the human hosts and the intervention technologies. The parasites are capable to continuously evolve and develop resistance to all new classes of antimalarial drugs. In south-east Asia, the emergence of parasites against Artemisinin and sensitivity to Artemisinin associated drugs have created major hazards for control and eradication of malaria. Novel strategies are required to keep track of the emergence of resistance; parasite specific polymorphic drugs are required to tackle drug responsiveness. Additional studies are required to identify optimal dosage strategies. In addition, understanding the role of mosquitoes in drug resistance mediation, development of mosquito containment steps can aid to detect spreading resistance enabling regional and global eradication of malaria. Anti-malarial drug resistance is an extremely important threat, that if overlooked can be detrimental for malaria eradication programs. Currently, ACT combination therapy appears to be effective in most malaria cases, however the reports of *in vitro* resistance against these agents has already been published and thus the probability of resistance to ACT combination therapy may be a likely situation. In this scenario, there is an unequivocal call for designing and developing new anti-malarial agents with novel mechanism of action.

MEDICINAL PLANTS WITH ANTIMALARIAL ACTIVITY

India possesses one of the World's richest biodiversity regions having around 8000 species of plants being reported so far. The list contains several medicinal plants that have been evaluated for their anti-malarial potential. These plants are known by various local names and are used by traditional healers for curing various diseases including malaria. The vast knowledge about these plants is still un-documented as it is transmitted through oral tradition. Approximately 1800 species are systematically documented in the coded Indian medicinal system, such as Ayurveda, Greek and Siddha, which have been expressed in many research manuscripts. Many herbal formulations have been described in local cultures and traditional medical literature with their use (Ugandhar *et al.,* 2014). Based on the literature review, around 76 species of plants are being used by different healers in rural and forest pockets of India for treating malaria. These anti-malarial plants have been documented and evaluated for *in vitro* and *in vivo* anti-malarial properties with different outcomes.

NATURAL COMPOUNDS AS A SOURCE FOR ANTIMALARIAL DRUGS

Natural products, including medicinal plants are active ingredients in the traditional medicine for the treatment of several diseases including malaria for thousands of years. There are several benefits associated with the natural products such as safety, efficacy, low cost and availability. The two major anti-malarial drugs quinine and artemisinin have been derived from medicinal plants. The studies related to the anti-malarial efficacy of natural products are quite expedient and are need to be further undertaken. A lot of medicinal plants have been characterized for having anti-malarial activity. The most important and diverse bio-potency is seen in alkaloids, flavonoids, terpenes, quasinoids and lactone. Some of the plants and compounds with such activity are discussed below.

Andrographis Paniculata (Burm. F.) Nees (Acanthaceae)

It is used extensively in the Indian traditional medicinal system as a hepatoprotective and a hepatostimulant agent and has been undertaken for analysis by several researchers. The plant has been shown to be efficacious in vitro and in vivo and the results open up several avenues for future development of isolated compound as a new anti-malarial drug candidates (Mishra *et al.,* 2011). Methanol, ethanol, chloroform, n-Hexane, and aqueous extracts of the plant have been characterized for anti-malarial potential against *P. falciparum*. *A. paniculata* plant extracts have many bioactive

Table 2. List of plants used for treatment of malaria by traditional healers

Botanical name of plants (Voucher number)	Vernacular (local) name	Family	Part(s) used	Active compounds	Reference
Andrographis paniculata (Burm.f.) Nees	Chiraeta/ Kalmegh	Acanthaceae	All parts	Deoxyandrographolide, neoandrographolide, 5,5'-dihydroxy-7,8,2'-trimetroxyflavone, 5- hydroxy-7,8,2',6'-tetramethoxyflavone, 5-hydroxy-7,8-dimethoxyflavanone, 5-hydroxy-7,8-dimethoxyflavone, 5,2'-dihydroxy-7,8- dimethoxyflavone, 5-hydroxy-7,8,2',5'-tetramethoxyflavone, 5-hydroxy-7,8,2',3'- tetramethoxyflavone, 5-hydroxy-7,8,2'-trimethoxyflavone, 5,4'-dihydroxy-7,8,2',3'-tetramethoxyflavone, dihydroneobaicalein, andrographidine A, andrographidine B, andrographidine C -Dglucopyranoside; andrograpanin,β-and 5,2'-dihydroxy-7,8-dimethoxyflavone 2'-O-neoandrographolide and andrographolide	(M.K. Dwivedi et al., 2019; Pholphana N, et al., 2004)
Azadirachta indica A.Juss.	Neem	Meliaceae	Root, Leaves, fruits	Azadirachtin Quercetin, 6-sitosterol, nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol, amino acid, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, azadirone, dihydrogedunin, neemfrutin A, spicatin, and desmethylllimocin B	(M.K. Dwivedi et al., 2019; M. A. Hossain, M. D. Shah & M. M. S.2011)
Acacia farnesiana (L.) Wild	Tarua kadam (Ass)	Mimosaceae	Bark	Albumin, gallic acid, glutelins, kaempferol, quercetin, methyl gallate, myricetin, naringenin, diosmetin, apigenin, catechin, ellagic acid, lupeol, α-amyrin, β-amyrin, β-sitosterol, ferulic and caffeic acids	(Delgadillo Puga Claudia et al., 2018)
Acorus calamus L.	Bach (Beng), Sweet flag (Eng)	*Araceae*	Rhizome	1 beta, 7 alpha (H)-cadinane-4 alpha, 6 alpha, 10 alpha-triol, 1 alpha, 5 beta-guaiane-10 alpha-O-ethyl-4 beta, 6 beta-diol and 6 beta, 7 beta (H)-cadinane-1 alpha, 4 alpha, 10 alpha-triol, sesquiterpenes, cadinane, 1-hydroxy-7, 9-guaiadien-8-one, calamenone, cis-asarone, chrysophanol, physcion, emodin and (+)-galbacin	(Zhu, M.,et al. , 2010)
Adhatoda zeylanica Medicus	Kawldai (Mi)	*Acanthaceae*	Leaf	Vasicine, vasicinine, 13-sitosterol, kaempferol, carotene vasakin, vasicinol 1-q-hydroxyvasicine, vasicinone, vasicol, beta-sophoroside, luteolin, adhtodic acid, vasicinolone, adhatodine, amisidine, vasicolone, vasicolinone and tritriacontane	(Rahaman AU, et al., 1997)
Alstonia scholaris R.Br.	Tun tong (Khamti), Chatiana (Assamese), Thamrita (Mi	*Apocynaceae*	Bark	Lagumanine (19 - hydroxytubotaiwine), angustilobine B acid, losbanine (6,7-seco-6-nor-angustilobine B), tubotaiwine, 6,7-secoangustilobine B, 17-O-Acetyl echtamine, echitamine, manilamine, N4-methyl angustilobine B, vallesamine, angustilobine tubotaiwine, 19-epischolaricine, Nb-methylscholarcine, Na-methylburmamine, vallesamine, picrinine, nareline, alschomine, angustilobine, 17-O-acetyl- Nb- demethyl echitamine, echitamidine-N-Oxide, echitaminic acid, sweroside, echitamidine, Nb-demethyl echitamine, 20-epi-19-echitamidine, N-b-demethylechitamine-N- oxide, villalstonine and macrocarpamine	(Patrick AG, et al., 2005)
Artemisia nilagirica (C.B. Clarke) Pamp.	Koken (Nyishi), Sai (Mi), Laibakngou (Man), Nagdona, Tongtoti (Ass)	*Asteraceae*	Leaf	Camphor, alpha-thujone, germacrene D, 1,8-cineol, beta-thujone, alpha-caryophyllene, 4-terpineol, camphene, borneol, 1,8-cineole, alpha-fenchene, sabinene, davanone B, alpha-humulene, myrcene and p-cymene	(Sushil Chandra Satia,et al., 2013)
Asplenium adiantoides C. Chr.	Ruimangma	Aspleniaceae	Whole Plant	-	(Rama Shankar, Sourabh Deb & B. K. S., 2012)
Aster ametlus L.	-	Asteraceae	Root	Sesquiterpene hydrocarbons, germacrene D, β-pinene, (E)-caryophyllene, β-germacrene, bicyclogermacrene	(Nemanja Rajčević et al., 2015)
Berberis aristata DC.	Daru Haridra (S), Drauhaldi (Beng)	Berberidaceae	Root	Barberine, oxyberberine, berbamine, aromoline, karachine, palmatine, oxyacanthine, taxilamine epiberberine, dehydrocaroline, jatrorrhizine, dihyrokarachine, columbamine, pakistanine, 1-O methyl pakistanine, pseudopalmatine chloride and pseudoberberine chloride	(Saied S & Batool S, 2007)
Betula alnoides Buch.-Ham	Hriang (Mi), Bhujpattra (Hi)	Betulaceae	Bark	Methyl salicylate, alpha-pinene (trace), beta-pinene (trace), limonene (trace), linalool (trace), alpha-terpineol (trace), camphor (trace)	(Nguyen Xuan Dung, 1995)
Brucea javanica (Linn.) Merr	Heining (Man), Tammu (Rongmei	Simaroubaceae	Fruit	(Z)-9- octadecenoic acid methyl ester, nhexadecanoic acid methyl ester, fatty acids, terpenes, (Z, Z)-9, 12- octadecadienoic acid, 1, 2, 3, 5- tetraisopropyl-cyclohexan, lactones, sterides, 4, 8, 12, 16-tetramethylheptadecan-4-olide, methyl 2-hydroxyhexadecanoate, lupeol acetate, methyl cis-9, 10- epoxyoctadecanoate, β-sitosterol, stigmasterol, 5α,- stigmastane-3,6-dione, methyl 9,10-dihydroxyoctadecanoate and 22- stigmasten-3-one, 1-O-hexadecanoyl-3-O-(9Z-octadecenoyl) glycerol, vanillin and thujopsene	(Zhiwei Su,et al., 2013)
Carica papaya L.	Papeya (Beng), Papaya	Caricaceae	Leaf	Papain, chymopapain, cystatin, tocopherol, ascorbic acid, flavonoids, cyanogenic glucosides, glucosinolates, carpaine and pseudocarpine	(Suhas J. Vyas,et al., 2014)
Cinchona officinalis Linn f.	-	Rubiaceae	Bark	Quinine, quinidine, cinchonidine, cinchonine, quinic acid, cinchotannic acid, quinovin, quinovine, quinovaic acid and quinovose (isohodesee)	(Pranay Gurung & Puspal De, 2017)
Cinnamomum bejolghota (Buch.-Ham)	*Tezpta* (Mi)	Lauraceae	Bark and leaf	1,8-cineole, γ-terpineol, borneol, terpinen-4-ol, α-pinene, Z-cinnamaldehyde, o-amyl cinnamyl alcohol, E-isoamyl cinnamate, E-2-hexyl cinnamaldehyde, benzyl cinnamate and phenethyl cinnamate	(Piyamas Atiphasawon, Sakon Monggoot & Sakon Monggoot, 2017)
Caesalpinia bonduc (L.) Roxb.	Gattaran	Caesalpiniaceae	All parts	Caesalpiniainone, 6-Omethylcaesalpiniainone, A, 6O -O-acetylloganic acid, 4O -O-acetylloganic acid, and 2-O-b-D-glucosyloxy-4-methoxybenzenepropanoic acid	(M.K. Dwivedi et al., 2019; Athar Ata & Elikana M. Gale, 2009)
Cassia tora L.	Chakoda	Caesalpiniaceae	Root, seed	Anthroquinones, chrysophanol,Emodin, obtusifolin, obtusin, chryso-obtusin, auranto-obtusin, nathoprynones, rubrofusarin, norubrofusarin, rubrofusaring, elicibioside, toralactone, torachrysone, 1, 3, 5-trihydroxy-6-7-dimethoxy-2-methylenglthroquinone, beta-sitosterol, apho-alpha-pyronetoralactune, chrysophanol, physcion, emodin, nuubrofusarin, chrysophonic acid-9-anthrone, emodinricotanstimasterol beta-sitosterol-beta D glucoside, ferindien, palmitic, stearic, succinic, dtartaric acid, uridin, quetoitrin and isoquecitrinhave	(M.K. Dwivedi et al., 2019; Swati Supare, 2015)
Cissampelos pareira L.	Padhin	Menispermaceae	Root, leaves	Hayatine, hayatinine, hayatidine ,cissampareine (b)-isochondodendrine, cissamine, magnifiorine. pareirubrines A and B, grandirubrine and isoimerubrine	(M.K. Dwivedi et al., 2019; S.K. Jain & Swadesh kumar Ahirwar, 2015)
Citrullus colocynthis (L.) Schrad.	Indrawan	Cucurbitaceae	Root	Colocynthein, myristic, palmitic, stearic, oleic, linoleic, linolenic acid, fatty acid, iso-vitexin, iso-orientin, iso-orientin 3-methylether, C-p-hydroxy benzyl	(M.K. Dwivedi et al., 2019; Gurudeeban S, Satyavani K, & R. T., 2010)
Citrus medica L.	Baranimbu (Beng)	Rutaceae	Fruit	Geranial, neral, β-pinene, α-pinene, citropten, α-Myroene, β-Phellandrene, Limonene (E)-β-Ocimene, Linalool, Citronellal and Eicosane	(Federica Menichinia ,et al., 2011)
Citrus sinensis (L.) Osbeck	Musambi, Sweet orange Serthium, Kamalanimbu	Rutaceae	Leaf	Hesperetin, naringin, tangeretin, nobiletin, chrysoeriol, limocitrin, limocitrol, quercetagetin, naringenin, sosakuranetin, sakuratin, 3,5,4'-Trihydroxy-7, 3' -dimethoxy-flavanone-glc, hesperetin, narirutin 4'-glucoside and narirutin	(Juan Manuel J. Favela-Hernández,et al., 2016)
Clausena excavata Burm. f.	Bhant	Rutaceae	Leaf	Binorponcitrin, xanthoxyletin, dentatin, nordentatin, clausenidin, scopoletin, dictamine, clausine D, clausine F, murrayafoline A, murrayanine, clausozoline, 2-hydroxy-3-formyl-7-methoxycarbazole, 3-formyl-2,7-dimethoxycarbazole, clausozoline J, clausine H, murrayacine and heptaphylline	(Tawanun Sripisut,et al., 2012)
Clerodendron infortunatum Gaertn	-	Verbenaceae	Root and leaf	Lenoleic, oleic, stearic, lignoceric acid, lupeol, β-sitosterol, 5, 25- sigmastadien, 3β-ol, lup_20(30)-en3β-diol-12-one, 3β-hydroxylup an-12-one, acteoside, fumaric acid, methyl and methyl esters of caffeic acid, apegerin, acacetin, hidpidulin, clerodin, lactose, glucose and fructose	(Singhmura saroji, 2016)
Clerodendrum colebrookianum Walp	Nephaphu	Verbenaceae	Leaf	Serraturnin A, serratoside A, serratoside B, 7-O-p-coumaroylcoyoglandoside, monomelittoside melittoside, sammangaoside C, sammangaoside A, sammangaoside B, mandarone , mandarone B, mandarone C, croleroden drum A, bungone A, bungone B, inerme A, inerme B	(Jin-Hui Wanga,e.et al., 2018).
Clerodendrum serratum (L.) Moon	Barangi	Verbenaceae	Root, leaf	α-spinasterol, (+) – catechin, luteolin, luteolin-7-O-β-D-glucuronide, apigenin, baicalein, scutellarein, 6-hydroxyluteolin, caffeic, ferulic acids, arabinose, glucuronic acid and D-mannitol	(Poornima BS,et al., 2015)
Coptis teeta Wall	Mishmi teeta	Ranunculaceae	Root, rhizome	1,2,3, Propametriol, 1-ethyl-2-pyrrolidinone, 8-nonenoic-8,9-D2 acid, methyl ester, DL-Valine, N-acetyl-, methyl ester, Benzenepropanoic acid, methyl ester, 4,6-heptadeconoic acid,3,3,6-trimethyl - , methyl ester, Bicyclo(5.2.0)Nonane, 4,8,8-trimethyl -2-methylene, 2-methoxy-4-venylphenol, Phenol,2,6-dimethoxy, Cysteamine Sulfonic Acid, 2-propenoic acid, 3-phenyl, methyl ester, (Z), 7-isopropqphenyl-4A-Methyl-1-methylenedecahydronphthalene, 1,3-benzenedicarboxylic acid, dimethyl ester, Nonanoic acid Methyl ester Benzoic acid, 4 Hydroxy-3-methoxy-, methyl ester	(Temin Payum, 2017)
Crotolaria occulta Grab	-	Fabaceae	Whole Plant	Stearic acid, oleic acid, linoleic acid, caprylic, margaric, capric, lauric, myristic, arachidonic, erucic and lignoceric acids	(M.O. Aremu, T. O. B. & J. A. A., 2012)
Croton tiglium L.	Jaiphal	Euphorbiaceae	Leaf, flower	bis(2,3-dihydroxypropyl) nonanedioate, 12-O-(o-methyl)butyrylphorbol-13-decanoate, 12-O-tigylphorbol-13-decanoate, (9S, 10R,11E,13R)-9,10,13-trihydroxyoctadec-11-enoic acid, methyl (9S, 10R,11E,13R)-9,10,13-trihydroxyoctadec-11-enoate, 4(1H)-quinolinone, and 5-hydroxy-2-pyridinemethanol, 4-deoxy-4 β phorbol diester	(Simran Sinsinwar, 2016)
Croton caudatus Geisel	-	Euphorbiaceae	Root	3,5,6,7,8,3',4'-heptamethoxyflavone, tangeretin, nobiletin, sinensetin, kaempferol, tiliroside, kaempferol-3-O-rutinoside and rutin	(Guo-An Zou,et al., 2010)
Cynoglossum glochidiion Wall.	Nyumli Mento	Boraginaceae	Root	-	(Rama Shankar, Sourabh Deb & B. K. S., 2012)
Datura metel L.	Dhatura	Solanaceae	Seed	Yanginhualine A, grasshopper ketone, cibroside A, vomifoliol, (6S,9R)-6-hydroxy-3-oxo-α-ionol-9-O-β-D-glucopyranoside, palmitic acid, stearic acid, oleic acid, linoleic acid, palmitoilc acid, ethyl palmitate	(M.K. Dwivedi et al., 2019; Ali Esmail Al-Snafi, 2017)
Dichroa febrifuga Lour.	Khawsik-damdawl, Basak	Saxifragaceae		-	(Rama Shankar, Sourabh Deb & B. K. S., 2012)
Elsholtzia blanda Benth	*Papil Nandung, Pheiri* (Tankhul), *Ban tulsi*	Lamiaceae	Leaf	Geranyl acetate, linalool, limonene, 1,8-cineole, acetophenone, bornyl acetate, camphene, α-pinene, borneol	(Hans Jürgen Bestmann, 1992)
Gomphostemma parviflora Wall.	-	Lamiaceae	Leaf	-	(Rama Shankar, Sourabh Deb & B. K. S., 2012)
Halenia elliptica D. Don	Qing ye dan	Gentianaceae	Whole Plant	1, 5-dihydroxy2, 3, 4-trimethoxyxanthone, xanthone glycosides, secoiridoid glucosides, xanthone-1-O-primeveroside, 2, 3, 4, 7-tetramethoxyxanthone-1-O-primeveroside, 2,3,5-trimethoxyxanthone-1-O-primeverosite, luteolin, apigenin and gentiopicroside	(D. Don Yu-Wei Suna, 2011)

compounds such as andrographolide, neoandrographolide, 14-deoxyandrographolide, andrographiside, isoandrographolide, andrograpanin, andrographic acid etc. (Sareer *et al.,* 2014). Andrographolide is a diterpenoid lactone belonging to isoprenoid family and is the main bioactive constituent of the stem and leaves of *A. paniculata*. Increased anti-malarial efficacy of *A. paniculata* extracts have been reported when combined with curcumin as evident with the IC_{50} values (7.2µg/ml) obtained for *A. paniculata* extract. Increased *in vivo* potency was also observed in the plant extract curcumin combination as compared to the extract or curcumin alone.

Andrographolide isolated from bark displayed potent activity when administered in combination with curcumin or artesunate in murine model (Mishra *et al.,* 2011). Andrographolide has emerged as a potent anti-malarial lead compound, however further pharmacological and toxicological studies are required for its validation as a potent drug. Rapid drug resistance is being reported to most of the anti-malarial drugs in response to increasing drug pressure (Carraz *et al.*, 2006). The resistance can also emerge against the current artemisinin-based combination therapy (ACT) which is currently the gold standard for malaria treatment. Novel combination including andrographolide in combination with other molecules such as curcumin or artesunate can lead way for the development of herbal formulation or design of novel molecules based on the andrographolide structure.

Picrasma Javanica Blume (Simaroubaceae)

P. javanica is known for its secondary metabolites which possesses several pharmacological and biological properties. The bark off the tree has been traditionally used for the treatment of malaria in Indonesia, Myanmar and Thailand. Different bark extracts have been evaluated with chloroform extract displaying significant level of *in vitro* anti-malarial activity against *P. falciparum* asexual stage. Two isolated compounds in the class of 1-substituted-4-oxygenated-β-carbolines, 6-hydroxy-4-methoxy-1-vinyl-β-carboline and 4-methoxy-1-vinyl-β- carboline displayed mean IC_{50} of 2.4 µg/ml and 3.2 µg/ml respectively (Pavanand *et al.*, 1988).

Saiin *et al.*, (2003) evaluated the *in vitro* anti-malarial activities against *P. falciparum* K1 strain and found the hexane extract with enhanced activity having IC_{50} values of 3.3µg/ml. The major compound isolated from the active extract was β-sitosterol that might be responsible for the activity. The same group (Saiin *et al.*, 2016) evaluated the *in vitro* activity of chloroform extract that contained 4-methoxy-1-vinyl-β- carboline, its derivative 1-ethyl-4-methoxy- β-carboline and Javacarboline that might be responsible for activity against *P. falciparum* K1. The group has isolated fourteen indole alkaloids from *P. javanica* (Chalerm & Sirithunyalug, 2017).

The anti-malarial activity of these β-Carboline alkaloids was not strong as compared to the current drugs that are in use clinically. These β-Carboline alkaloids

Figure 1. Molecules with potent anti-malarial activity

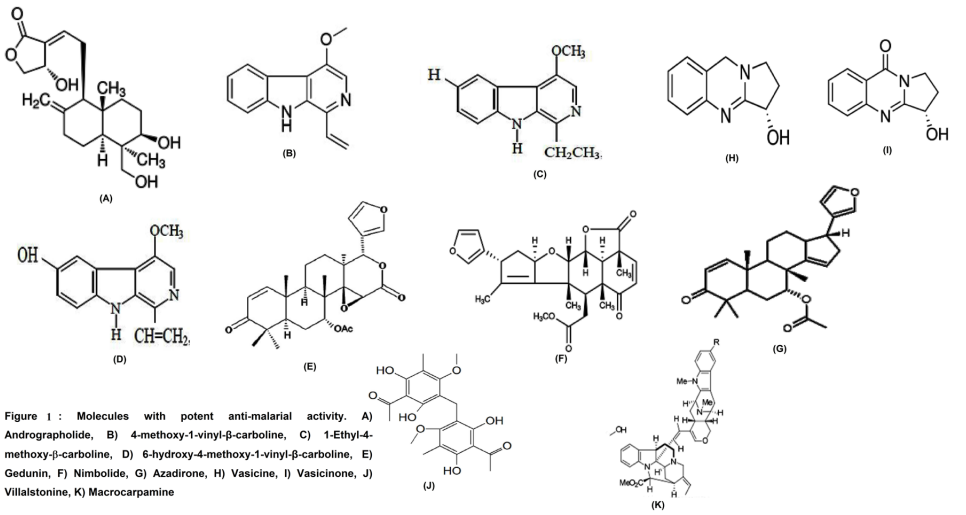


Figure 1 : Molecules with potent anti-malarial activity. A) Andrographolide, B) 4-methoxy-1-vinyl-β-carboline, C) 1-Ethyl-4-methoxy-β-carboline, D) 6-hydroxy-4-methoxy-1-vinyl-β-carboline, E) Gedunin, F) Nimbolide, G) Azadirone, H) Vasicine, I) Vasicinone, J) Villalstonine, K) Macrocarpamine

were transformed into π-delocalized lipophilic cationic (DLC) structures and were analyzed for *in vitro* activity against *P. falciparum*. Derivatives with a methyl or ethyl group on the pyridine nitrogen atom resulted in a fivefold and a thirty nine fold increase in anti-malarial activities, respectively with decreased cytotoxicity levels. On transforming carboline 1 to carbolinium salts 5, a sixty seven fold increase in anti-malarial activity was observed as compared to the parent salt. The result clearly indicate that DLC compounds have enhanced anti-malarial activities within the class of β-carbolines (Takasu *et al.*, 2004). Transformation of selective compounds into a DLC structure can provide us with novel compounds with enhanced anti-malarial activities.

Azadirachta Indica A. Juss. (Meliaceae)

A. indica is an evergreen, fast-growing native Indian plant that has been extensively introduced in most of the tropical and subtropical regions. It is of great medicinal value and has been used widely in Chinese, Ayurvedic, and Unani systems of medicines (Pallav *et al.,* 2014). Different parts of this plant including seeds, leaves, barks and fruits are frequently used for the treating malaria and other vector borne disease. *A. indica* is known to possess around 100 different limonoids due to which citrus fruits are bitter in nature. The compounds are highly oxygenated, modified terpenoids having wide spectrum of biological activities including anti-malarial. Nimbolide, gedunin, nimbin and other limonoids purified from *A. indica* and other medicinal plants are known to display *in vitro* anti-malarial activities (Roy &

Saraf, 2006). Nimbolide and terpenoid lactone were found to inhibit *P. falciparum in vitro* having EC_{50} values of 2.0μM (Rochanakij & Thebtaranonth, 1985). Ten pure triterpenoid derivatives including neem fruitins-A and B were purified from the African sample of *A. indica* and were analyzed *in vitro* against chloroquine sensitive D10 and chloroquine resistant W2 strains of *P. falciparum* carrying the pLDH assay. The tested compounds were more active on the chloroquine-resistant clone (W2). The most active compounds were azadirone (IC_{50} 1.21±0.30μM), gedunin and neemfruitin A. The ethyl alcohol and butanol fractions also displayed substantial anti-plasmodial activity with IC_{50} values in the range of 1.31-3.35 μg/mL (Chianese *et al.*, 2010).

Justicia Adhatoda Linn. (Acanthaceae)

Justicia adhatoda has been reported to have antimicrobial, anti-tussive, abortifacient, tuberculosis, antiinflammatory, hypoglycemic activity, hepatoprotective effect, antioxidant effect and antiulcer activities. The leaves are known to contain many compounds such as vasicinone, vasicine, adhatodine, anisotine, vasicoline, vasicolinone, adhavasinone, vasicinolone, hydroxypeganine and adhavasine. The *in vitro* anti-plasmodial activity of vasicinone, vasicine and semi-synthetic derivatives (VA-1) was reported against cultured *P. falciparum*. The compounds were active against *P. falciparum* with vasicine displaying IC_{50}= 89.8 μg/mL and vasicinone had IC_{50}=38.9 μg/mL (Gopalan *et al*., 2016).

Alstonia Scholaris (Linn.) R. Br. and *Alstonia Macrophylla* Wall. (Apocynaceae)

This plant is called as devils tree, dita bark tree is an active component in traditional medicinal systems from a long time to cure various human ailments. It is found throughout India in the deciduous and evergreen forests (Dey, 2011). Extracts of three Thai *Alstonia* species, A. scholaris, *A. macrophylla* and *A. glaucescens* (Monach.) were evaluated for anti-plasmodial activity. Methanolic extract of *A. macrophylla* bark exhibited an IC_{50} value of 5.7 μg/ml. 13 alkaloids purified from this active extract were found to display profound activities against the K1 and T9-96 (chloroquine-sensitive) strains of *P. falciparum* (Keawpradub *et al*., 1999). Prominent anti-plasmodial activity were exhibited by the root and stem barks extracts of *A. macrophylla* having the mean IC_{50} values of 5.7 and 12.8mg/ml, respectively. Based on activity-directed fractionation of the *A. macrophylla* root bark extract, 13 Corynantheane-type indoles were purified and evaluated. Among the tested alkaloids eight displayed IC_{50} values greater than 5mM. Enhanced anti-plasmodial activities against *P. falciparum* K1 strain were observed mainly amongst bisindole

alkaloids. The monomeric indole, 2 (pleiocarpamine) displayed maximum activity having an IC_{50} value of 6.44mM which was about 32 times less potent than standard chloroquine diphosphate. IC_{50} values of the macrolinepleiocarpamine bisindoles, villalstonine (0.27 mM) and macrocarpamine (0.36mM) were found to be significant. These activities can be further enhanced by increasing the lipophilicity that could facilitate the transport of these molecules across the cell membranes of the red blood cells and the malarial parasites.

COMMERCIALIZED NATURAL PRODUCTS

Andrographis paniculata is amongst one of the most valuable medicinal plant containing diterpene lactones that have been known to possess several pharmacological activities. Currently, the plant extracts of *A. paniculata* are commercially available in tablets or injection forms in some countries such as Chicago and China. In China, the tablets are sold under different brand names such as Kan Jang, Chuanxinlian, Xiaoyan Lidan and Chuanxinlian anti-phologistic tablets (Yeung & Yao, 1987) or as injectables under the brand name Yamdepieng and Chuanxinlian Ruangas. Andrographolide, deoxyandrographolide and neoandrographolide are the active ingredients in such products (Zhoa *et al.,* 2002). Ayush-64 is an Indian Ayurvedic drug combination having four components. The combination is available as tablets with an suggested dose of 1g/day for five to seven days at an affordable cost of fourteen rupees (Valecha *et al*., 2000). But due to low effective rate (48.9%) as compared to chloroquine it is not recommended for treatment regimens. Identification, purification and optimization of the active components is further required for development of more potent compounds (Willcox & Bodeber, 2004).

FUTURE RESEARCH THRUST

There is an urgent requirement for the discovery and development of new drug leads and novel drug targets due to the emerging threat of drug resistance. Natural product scaffolds have been utilized for the development of the almost all anti-malarial drugs developed so far. With the involvement of medicinal chemistry, combination therapy and novel assay development programs there are several new formulations in the fight against malaria.

New drug targets with novel mode of action need to be identified and validated. Drug assays need to be developed for screening millions of compounds with the aim of identifying new start points for drug discovery programs. There has been significant advancement in image processing and automation technologies that

allow the high throughput screening assays for live parasites inside human host cells. Developing such assays would make the screening programs many times faster and cheaper as previously done. Addressing the problem of drug resistance, the new hits need to be characterized for their activity against existing drug-resistant parasites.

Till date there are 25,000 different pure compounds with less than 1μm *in vitro* effectiveness against the parasite that binds to around thousand different scaffolds. These molecules need to be evaluated for their toxicity analysis and rapidly advanced to clinical trials. There has been unprecedented advancement in the analytical methodologies that allow detailed characterization of the plant material by advanced spectroscopic methods. Combination of these approaches with availability of large amounts of proteomics, transcriptomics, xenobiotic and metabolomics data offers the possibility for the identification of novel drug targets and lead molecules. Traditional medicinal systems are required to be accepted by the national authorities along with the international organizations like US-FDA and the WHO. Since communities are using the herbal medicines worldwide for a considerably large period of time, there is a responsibility on the scientific organizations to understand them, accept them and prepare guidelines for their preparation, usage and safety so that the traditional system of medicine may recognition.

CONCLUSION

Malaria is a vector borne parasitic tropical disease endemic in ninety one countries. With the emergence of drug resistance, high cost of artemisinin-based combination therapies, the hope lies in the traditional medicinal system that can be the sustainable answer for malaria treatment. Since ancient times natural products are the key players in the anti-malarial drug discovery programs. Large number of plant species has been reported to possess anti malarial activities by various medicinal systems. The current anti-malarial therapy consists of the natural products and related derivatives (quinine, chloroquine, mefloquine, ART (qinghaosu), arteether, artemether and artesunate). Till date numerous natural products with potent anti-malarial activity have been described but scientific validation of them is required. Guidelines for establishing the efficacy and safety of traditional medicines are required. The active constituents present in different extracts or formulation are needed to be isolated in order to identify the lead molecules for characterization as modern drugs and establishment of reliable quality control measures before their release into the market. Nature due to its high diversity has the capacity to provide us with the solutions to all diseases in the form of natural products that needs to be identified and developed as novel drugs.

REFERENCES

Achan, J., Talisuna, A. O., Erhart, A., Yeka, A., Tibenderana, J. K., Baliraine, F. N., ... D'Alessandro, U. (2011). Quinine, an old anti-malarial drug in amodern world: Role in the treatment of malaria. *Malaria Journal*, *10*(1), 144. doi:10.1186/1475-2875-10-144 PMID:21609473

Alifrangis, M., Nag, S., Schousboe, M. L., Ishengoma, D., Lusingu, J., Pota, H., ... Cox, J. (2014). Independent origin of *Plasmodium falciparum* antifolate super-resistance, Uganda, Tanzania, and Ethiopia. *Emerging Infectious Diseases*, *20*(8), 1280–1286. doi:10.3201/eid2008.131897 PMID:25061906

Baird, J. K. (2009). Resistance to therapies for infection by *Plasmodium vivax. Clinical Microbiology Reviews*, *22*(3), 508–534. doi:10.1128/CMR.00008-09 PMID:19597012

Bruce-Chwatt, L. J., Black, R. H., Canfield, C. J., Clyde, D. F., Peters, W., Wernsdorfer, W. H., & World Health Organization. (1986). *Chemotherapy of malaria*. WHO.

Carraz, M., Jossang, A., Franetich, J. F., Siau, A., Ciceron, L., Hannoun, L., & Mazier, D. (2006). A plant-derived morphinan as a novel lead compound active against malaria liver stages. *PLoS Medicine*, *3*(12), 2392–2402. doi:10.1371/journal.pmed.0030513 PMID:17194195

Chianese, G., Yerbanga, S. R., Lucantoni, L., Habluetzel, A., Basilico, N., Taramelli, D., ... Taglialatela-Scafati, O. (2010). Antiplasmodial triterpenoids from the fruits of neem, *Azadirachta indica. Journal of Natural Products*, *73*(8), 1448–1452. doi:10.1021/np100325q PMID:20669933

Cui, L., Wang, Z., Miao, J., Miao, M., Chandra, R., Jiang, H., & Cui, L. (2012). Mechanisms of in vitro resistance to dihydroartemisinin in *Plasmodium falciparum. Molecular Microbiology*, *86*(1), 111–128. doi:10.1111/j.1365-2958.2012.08180.x PMID:22812578

Da Silva, A. F., & Benchimol, J. L. (2014). Malaria and quinine resistance: A medical and scientific issue between Brazil and Germany (1907–19). *Medical History*, *58*(1), 1–26. doi:10.1017/mdh.2013.69 PMID:24331212

Deepak, A. S. A. (2008). *Indigenous Herbal Medicines: Tribal Formulations and Traditional Herbal Practices*. Jaipur, India: Aavishkar Publishers Distributor.

Demain, A. L. (2014). Importance of microbial natural products and the need to revitalize their discovery. *Journal of Industrial Microbiology & Biotechnology*, *41*(2), 185–201. doi:10.100710295-013-1325-z PMID:23990168

Deshpande, P. K., Gothalwal, R., & Pathak, A. K. (2014). Phytochemical analysis and evaluation of antimalarial activity of *Azadirachta indica. The Pharma Innovation*, *3*(9, Part A), 12.

Dey, A. (2011). Phytochemistry and pharmacology: A concise review. *Journal of Applied Pharmaceutical Science*, *1*(6), 51–57.

Dorsey, G., Kamya, M. R., Singh, A., & Rosenthal, P. J. (2001). Polymorphisms in the *Plasmodium falciparum* pfcrt and pfmdr-1 genes and clinical response to chloroquine in Kampala, Uganda. *The Journal of Infectious Diseases*, *183*(9), 1417–1420. doi:10.1086/319865 PMID:11294677

Favela-Hernández, J. M. J., González-Santiago, O., Ramírez-Cabrera, M. A., Esquivel-Ferriño, P. C., & Camacho-Corona, M. D. R. (2016). Chemistry and pharmacology of *Citrus sinensis. Molecules (Basel, Switzerland)*, *21*(2), 247. doi:10.3390/molecules21020247

Ganguly, S., Saha, P., Chatterjee, M., & Maji, A. K. (2014). Prevalence of polymorphisms in antifolate drug resistance molecular marker genes pvdhfr and pvdhps in clinical isolates of *Plasmodium vivax* from Kolkata, India. *Antimicrobial Agents and Chemotherapy*, *58*(1), 196–200. doi:10.1128/AAC.01171-13 PMID:24145518

Garcia, L. S. (2010). Malaria. *Clinics in Laboratory Medicine*, *30*(1), 93–129. doi:10.1016/j.cll.2009.10.001 PMID:20513543

Hurwitz, E. S., Johnson, D., & Campbell, C. C. (1981). Resistance of *Plasmodium falciparum* malaria to sulfadoxine-pyrimethamine ('Fansidar') in a refugee camp in Thailand. *Lancet*, *1*(8229), 1068–1070. doi:10.1016/S0140-6736(81)92239-X PMID:6112445

Imwong, M., Pukrittayakamee, S., Renia, L., Letourneur, F., Charlieu, J. P., Leartsakulpanich, U., ... Snounou, G. (2003). Novel point mutations in the dihydrofolate reductase gene of *Plasmodium vivax*: Evidence for sequential selection by drug pressure. *Antimicrobial Agents and Chemotherapy*, *47*(5), 1514–1521. doi:10.1128/AAC.47.5.1514-1521.2003 PMID:12709316

Jain, V., Basak, S., Bhandari, S., Bharti, P. K., Thomas, T., Singh, M. P., & Singh, N. (2014). Burden of complicated malaria in a densely forested Bastar region of Chhattisgarh State (central India). *PLoS One*, *9*(12), 115–266. doi:10.1371/journal.pone.0115266 PMID:25531373

Keawpradub, N., Kirby, G. C., Steele, J. C. P., & Houghton, P. J. (1999). Antiplasmodial activity of extracts and alkaloids of three Alstonia species from Thailand. *Planta Medica*, *65*(08), 690–694. doi:10.1055-1999-14043 PMID:10630106

Krogstad, D. J., Gluzman, I. Y., Kyle, D. E., Oduola, A. M., Martin, S. K., Milhous, W. K., & Schlesinger, P. H. (1987). Efflux of chloroquine from *Plasmodium falciparum*: Mechanism of chloroquine resistance. *Science*, *238*(4831), 1283–1285. doi:10.1126cience.3317830 PMID:3317830

Lemonnier, N., Zhou, G. B., Prasher, B., Mukerji, M., Chen, Z., Brahmachari, S. K., & Sagner, M. (2017). Traditional knowledge-based medicine: a review of history, principles, and relevance in the present context of P4 systems medicine. *Progress in Preventive Medicine, 2*(7), e0011.

Martin, S. K., Oduola, A. M., & Milhous, W. K. (1987). Reversal of chloroquine resistance in *Plasmodium falciparum* by verapamil. *Science*, *235*(4791), 899–901. doi:10.1126cience.3544220 PMID:3544220

Mazid, M., Khan, T. A., & Mohammad, F. (2012). Medicinal plants of rural India: A review of use by Indian folks. *Indo Global Journal of Pharmaceutical Sciences*, *2*(3), 286–304.

Mishra, K., Dash, A. P., & Dey, N. (2011). Andrographolide: A novel antimalarial diterpene lactone compound from *Andrographis paniculata* and its interaction with curcumin and artesunate. *Journal of Tropical Medicine*, *2011*(365645), 1–6. doi:10.1155/2011/579518 PMID:21760808

Musset, L., Bouchaud, O., Matheron, S., Massias, L., & Le Bras, J. (2006). Clinical atovaquone- proguanil resistance of Plasmodium falciparum associated with cytochrome b codon 268 mutations. *Microbes and Infection*, *8*(11), 2599–2604. doi:10.1016/j.micinf.2006.07.011 PMID:16962361

Naidoo, I., & Roper, C. (2013). Mapping 'partially resistant', 'fully resistant', and 'super resistant' malaria. *Trends in Parasitology*, *29*(10), 505–515. doi:10.1016/j.pt.2013.08.002 PMID:24028889

Nielsen, C. M., Vekemans, J., Lievens, M., Kester, K. E., Regules, J. A., & Ockenhouse, C. F. (2018). RTS, S malaria vaccine efficacy and immunogenicity during *Plasmodium falciparum* challenge is associated with HLA genotype. *Vaccine*, *36*(12), 1637–1642. doi:10.1016/j.vaccine.2018.01.069 PMID:29439870

Nkrumah, L. J., Riegelhaupt, P. M., Moura, P., Johnson, D. J., Patel, J., Hayton, K., ... Fidock, D. A. (2009). Probing the multifactorial basis of *Plasmodium falciparum* quinine resistance: Evidence for a strain-specific contribution of the sodium-proton exchanger PfNHE. *Molecular and Biochemical Parasitology*, *165*(2), 122–131. doi:10.1016/j.molbiopara.2009.01.011 PMID:19428659

Parija, S. P., & Praharaj, I. (2011). Drug resistance in malaria. *Indian Journal of Medical Microbiology*, *29*(3), 243–248. doi:10.4103/0255-0857.83906 PMID:21860103

Pavanand, K., Yongvanitchit, K., Webster, H. K., Dechatiwongse, T., Nutakul, W., Jewvachdamrongkul, Y., & Bansiddhi, J. (1988). *In vitro* antimalarial activity of a Thai medicinal plant *Picrasma javanica* Bl. *Phytotherapy Research*, *2*(1), 33–36. doi:10.1002/ptr.2650020105

Phyo, A. P., Nkhoma, S., Stepniewska, K., Ashley, E. A., Nair, S., McGready, R., ... Nosten, F. (2012). Emergence of artemisinin-resistant malaria on the western border of Thailand: A longitudinal study. *Lancet*, *379*(9830), 1960–1966. doi:10.1016/S0140-6736(12)60484-X PMID:22484134

Pringle, J. C., Carpi, G., Almagro-Garcia, J., Zhu, S. J., Kobayashi, T., Mulenga, M., & Norris, D. E. (2018). RTS, S/AS01 malaria vaccine mismatch observed among *Plasmodium falciparum* isolates from southern and central Africa and globally. *Scientific Reports*, *8*(1), 1–8. doi:10.103841598-018-24585-8 PMID:29700348

Rochanakij, S. U. D. A. R. A. T. A. N. A., Thebtaranonth, Y. O. D. H. A. T. H. I., Yenjai, C., & Yuthavong, Y. (1985). Nimbolide, a constituent of *Azadirachta indica*, inhibits Plasmodium falciparum in culture. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *16*(1), 66–72. PMID:3895455

Roper, C., Pearce, R., Nair, S., Sharp, B., Nosten, F., & Anderson, T. (2004). Intercontinental spread of pyrimethamine-resistant malaria. *Science*, *305*(5687), 1124. doi:10.1126cience.1098876 PMID:15326348

Roy, A., & Saraf, S. (2006). Overview of significant bioactive triterpenes distributed in plants kingdom. *Biological & Pharmaceutical Bulletin*, *29*(2), 191–201. doi:10.1248/bpb.29.191 PMID:16462017

Saiin, C., Rattanajak, R., Kamchonwongpaisan, S., Ingkaninan, K., Sukontason, K., Baramee, A., & Sirithunyalug, B. (2003). Isolation and *in vitro* antimalarial activity of hexane extract from Thai Picrasma javanica B1 stembark. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *34*(2), 51–55. PMID:19230571

Saiin, C., Sirithunyalug, B., Rattanajak, R., Kamchonwongpaisan, S., Baramee, A., Sukontason, K., & Ingkaninan, K. (2016). Isolation and in vitro antimalarial activity of chloroform extract from Thai Picrasma javanica Bl stembark. *Advancement in Medicinal Plant Research*, *4*(3), 94–98.

Sareer, O., Ahmad, S., & Umar, S. (2014). *Andrographis paniculata*: A critical appraisal of extraction, isolation and quantification of andrographolide and other active constituents. *Natural Product Research*, *28*(23), 2081–2101. doi:10.1080/14786419.2014.924004 PMID:24912126

Sen, S., & Chakroborty, R. (2015). Towards the integration and advancement of herbal medicines: A focus on traditional Indian medicine. *Botanics: Targets and Therapy*, *5*, 33–44. doi:10.2147/BTAT.S66308

Sinou, V., Pelleau, S., Huong, V. N., Huong, N. T., Bertaux, L., Desbordes, M., & Parzy, D. (2011). Polymorphism of Plasmodium falciparum Na+/H+ exchanger is indicative of a low in vitro quinine susceptibility in isolates from Viet Nam. *Malaria Journal*, *10*(1), 164. doi:10.1186/1475-2875-10-164 PMID:21669011

Syafruddin, D., Siregar, J. E., & Marzuki, S. (1999). Mutations in the cytochrome b gene of *Plasmodium berghei* conferring resistance to atovaquone. *Molecular and Biochemical Parasitology*, *104*(2), 185–194. doi:10.1016/S0166-6851(99)00148-6 PMID:10593174

Takala-Harrison, S., Clark, T. G., Jacob, C. G., Cummings, M. P., Miotto, O., Dondorp, A. M., & Bethell, D. (2013). Genetic loci associated with delayed clearance of *Plasmodium falciparum* following artemisinin treatment in Southeast Asia. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(1), 240–245. doi:10.1073/pnas.1211205110 PMID:23248304

Takasu, K., Shimogama, T., Saiin, C., Kim, H. S., Wataya, Y., & Ihara, M. (2004). π-Delocalized β- carbolinium cations as potential antimalarials. *Bioorganic & Medicinal Chemistry Letters*, *14*(7), 1689–1692. doi:10.1016/j.bmcl.2004.01.055 PMID:15026051

ter Kuile, F. O., van Eijk, A. M., & Filler, S. J. (2007). Effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy: A systematic review. *Journal of the American Medical Association*, *297*(23), 2603–2616. doi:10.1001/jama.297.23.2603 PMID:17579229

Tun, K. M., Imwong, M., Lwin, K. M., Win, A. A., Hlaing, T. M., Hlaing, T., & Dhorda, M. (2015). Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: A cross-sectional survey of the K13 molecular marker. *The Lancet. Infectious Diseases*, *15*(4), 415–421. doi:10.1016/S1473-3099(15)70032-0 PMID:25704894

Ugandhar, T., Chandraiah, G., & Devi, A. (2014). Studies on ethno-medicinal plants for womenfolk's health care in ramagiri fort of mahadevapur reserve forest in karimnagar district of telangana region. *Science Research Reporter*, *4*(1), 51–56.

Valecha, N., Devi, C. U., Joshi, H., & Shahi, V. K. (2000). Comparative efficacy of Ayush-64 vs chloroquine in *Vivax* malaria. *Current Science*, *78*, 1120–1122.

White, N. J. (2004). Antimalarial drug resistance. *The Journal of Clinical Investigation*, *113*(8), 1084–1092. doi:10.1172/JCI21682 PMID:15085184

White, N. J. (2009). Malaria. In G. C. Cook & A. I. Zumla (Eds.), *Manson's Tropical Diseases* (22nd ed.). Elsevier.

WHO. (2002). *Traditional Medicine: Growing Needs and Potentials*. WHO.

WHO. (2014). *World Malaria Report*. WHO.

WHO. (2018). *World Malaria Report*. WHO.

Willcox, M. L., & Bodeker, G. (2004). Traditional herbal medicines for malaria. *BMJ (Clinical Research Ed.)*, *329*(7475), 1156–1159. doi:10.1136/bmj.329.7475.1156 PMID:15539672

Wilson, R. J., & Williamson, D. H. (1997). Extrachromosomal DNA in the Apicomplexa. *Microbiology and Molecular Biology Reviews*, *61*(1), 1–16. doi:10.1128/.61.1.1-16.1997 PMID:9106361

Yeung, S. C. S., Yao, S. C., & Wang, L. L. (1987). Pharmacology and Application of China Materia Medica (Vol. 2). Academic Press.

Zhao, J., Yang, G., Liu, H., Wang, D., Song, X., & Chen, Y. (2002). Determination of andrographolide, deoxyandrographolide and neoandrographolide in the Chinese herb *Andrographis paniculata* by micellar electrokinetic capillary chromatography. *Phytochemical Analysis: An International Journal of Plant Chemical and Biochemical Techniques*, *13*(4), 222–227. doi:10.1002/pca.644 PMID:12184176

Chapter 9
Traditional Herbs With Potential Wound Healing Properties

Neelesh Babu
Gurukula Kangri Vishwavidyalaya, India

Ajeet Singh
https://orcid.org/0000-0002-4393-8889
National Dairy Research Institute, India

Navneet
Gurukula Kangri Vishwavidyalaya, India

ABSTRACT

Medicinal plants have been necessary to conventional and non-customary types of prescriptions dating back to somewhere around 5000 years ago. Researchers progressively depend on current logical techniques and proof-based medication to demonstrate the viability of herbal medicines and spotlight on a better comprehension of the systems of their activity. Notwithstanding, data concerning quantitative human health advantages on natural remedies is yet uncommon, constraining their legitimate valuation. Traditional medicines are regularly utilized for the wound-healing process covering a wide zone of various skin-related infections. This chapter will give information about the wound-healing capability of plants that are useful for the advancement of new wound-healing formulations.

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INTRODUCTION

India is the most extravagant nation in the world for its natural assets. From the ancient time larger part of the general population and network relies on customary prescription. Studies uncovered that plants are one of the major source of compounds that are bioactive and have antimicrobial, anticancer properties (Mallik, *et al.,* 2014). Plants are having incredible restorative significance for individuals because of their different pharmacological properties. Today, substantial numbers of medications are created from different plants which are dynamic against number of problems.

Although synthetic medications are broadly incorporated yet they create a few adverse symptoms to the users. At that point herbal prescriptions are successful because of nontoxic nature and furthermore microorganisms are nonresistant to them (Sarkar, *et al.,* 2013). Under this thought there is much developing enthusiasm to find novel herbal medications for the treatment of irresistible infections.

Wound can be simply defined as the breakdown of protective function of the skin and tissues. Its infection represents invasion of tissues by one or more species of microorganisms. Several medicinal plants have enormous capability in healing of wounds. The medicines which are prepared by these medicinal plants are reportedly safe and cost effective as compared to synthetic drugs; these are considered as good pharmaceuticals. These alternate medicines can combat with drug resistant microbes and exhibits strong disease curing potential. For example: *Aloe vera*, its gel constitutes of several enzymes, carbohydrates, amino acids, vitamins and minerals which gave prominent results in chronic wound management (Rodriguez *et al.,* 1988; Kaufman *et al.,* 1988).

Herbal Antimicrobial Agents Have Following Advantages

- Natural receptors are present in the human body for the plants bioactive compounds.
- Herbal antimicrobial agents are reportedly safe as compared to the synthetic drugs.
- It is difficult for the microbes to acquire resistance against herbal drugs.
- These herbal drugs are cost effective.

Considering these qualities of herbal drugs, several herbal pharmaceutical companies (e.g. Patanjali, Himalaya, Charak etc.) extensively manufacturing lots of herbal drugs for several medical conditions as possible. These include several drugs, ointments, antimicrobial agents for wound care and its healing.

WOUND INFECTION

As far as the largest organ of the human body has been concerned skin is named first which is made up of epidermis, dermis and subcutaneous tissues. Several vital functions are performed by the skin which includes protection against external factors (Kanitakis, 2002). The surface of skin is not sterile even when it is clean due to the presence of mixed community of microbes known as the normal microflora. Physical breakdown of the protective function results in wound i.e. the loss of the continuity of underlying connective tissues. Due to loss in continuity of this protective barrier pathogens are able to invade a tissue which leads to wound infection. From microbiological point of view "a wound infection is the result of physical disruption of the skin which leads to the contamination, colonization and infection by pathogens."

Number of factors contributes to pathogenicity of the microbes which can be easily influenced by genetic and environmental conditions. Virulence of the microbes is due to their enzyme production, structural features and the products formed by their metabolic process contribute to pathogenicity. The capsule containing bacteria (e.g. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) remain protected against complement activation as well as phagocytosis. Pili those are present in several bacteria (e.g. *Pseudomonas aeruginosa* and *Escherichia coli*) helps them for the attachment to the host cells. Cell wall of bacteria contains several polysaccharide compounds which help bacteria to adherence at extracellular matrix components (e.g. collagen) in host tissue.

Extracellular infection of the wound is more frequent than that of intracellular infection and most of the pathogens rely on the production of extracellular enzymes for the deep invasion of tissue. Damage of host cell or tissue also results due to the microbial toxins production i.e. endotoxins and exotoxins. Basically exotoxins are released by the bacteria that are viable, despite endotoxins are known to be integral components of the cell wall which are only released on the death of cell. Local as well as systemic effects can be caused by these toxins depending upon their dose (Moffatt, 2005).

People with Following Conditions are Susceptible to the Wound Infections

- Poor circulation
- Comorbidities
- Malignancy, rheumatoid arthritis, obesity, malnutrition
- Medication
- Psychosocial factors which includes poor hygiene and unhealthy lifestyle.

- Weak immune system
- Immobility (Carville, 2008).

MEDICINAL PLANTS IN INDIA WITH WOUND HEALING AND ANTIMICROBIAL PROPERTIES

The medicinal plants have been extensively utilized throughout the world in the areas of health and management. In India herbal drugs have been the premise of treatment and solution for the different ailments as well as physiological conditions in conventional practice, for example, Ayurveda. Therapeutic components of these plants are assumed to be very significant in conventional medications. Plants belonging to following families have scientifically proven antimicrobial activities.

Fabaceae

Tephrosia purpurea (Linn.)

T. purpurea is an erect; annually spreading, perennial herb which is occasionally bushy measuring 40-80 cm tall. In Ayurvedic literature *T. purpurea* named as "Sarwa wran vishapaha" which denotes its property to cure all kind of wounds. This herb contains several phytochemicals such as flavanones, glycosides, sterols, rotenoids, isoflavones, flavonoids and chalcones. In Ayurveda its several parts are utilized to treat impotency, respiratory disorders, diarrhea, gonorrhea, rheumatism and urinary tract infections. It has ability to treat disorders related to the heart, liver, blood, kidney and spleen. Whole plant is utilized as laxative, dried part has diuretic properties whereas roots and seeds are utilized as vermifuge, insecticidal and skin eruption. For the treatment of vomiting its decoction is utilized and its pods extract effectively utilized during inflammation and pain (Deshpande *et al.,* 2003; Babu *et al.,* 2017).

Wound Healing and Antimicrobial Activity

Screening of antibacterial activity of *T. purpurea* ethanolic root extract (R1 and R2) showed inhibitory effects on three *Pseudomonas* strains and two of the *E. coli* strains among all the tested microbes (Rangama *et al.,* 2009). Laishram *et al.,* (2013) screened antimicrobial efficacy of methanolic and ethanolic extracts of this herb against both gram positive and gram negative bacteria including some fungal species. Moderate activity was observed by both of the extract which was dose dependent and increases with increase in the extracts concentration ranging from 25 to 100 mg/ml.

Pongamia pinnata (Linn.) Pierre

This medium size plant is fast growing with average size measuring 30-40 f. long having spread canopy. This plant comprises of short trunk with diameter measuring around 1.64 f. Its leaves are 5-10 cm long and 4-6 cm wide and assembled in 5-7 leaflets. Flowers are pink to light purple sometimes white in colour with pea shaped morphology. Its pod shells are elliptical in shape measuring 3-6 cm long and 4-6 cm wide contains only one seed. It prefers to grow in alkaline to salty, clay, sandy and gravelly soil (Halder, *et al.,* 2014). Traditionally it is enormously utilized in the treatment of wounds, inflammation, ulcers, skin infections and piles as folk medicine.

Wound Healing and Antimicrobial Activity

Methanolic leaves extract gave inhibitory effect on various microbes that includes *E. aerogenes, Candida albicans, P. aeruginosa, E. coli, S. pyogens, S. typhi, A. niger, S. epidermis,* and *Micrococcus luteus.* Inhibition varies from one organism to other (Dwivedi *et al.,* 2017).

Glycyrrhiza glabra (Linn.)

G. glabra is one of the most important herbs used as flavoring agent as well as a potent medicine in Ayurveda. Traditionally it is utilized for the treatment of duodenal and gastric ulcers, dyspepsia, and antiviral agent. It is effectively used against anemia, gout sore throat, tonsillitis, flatulent, skin diseases etc. (Damle, 2014).

Wound Healing and Antimicrobial Activity

Methanol extracted *G. glabra* gave fungicidal activity against *Chaetomium funicola* and *Athrinium sacchari* (Hojo & Sato, 2002). Its ethanolic extract shows antibacterial activity against *S. aureus* and *S. pyogens* (Zadeh *et al.,* 2013).

Acacia nilotica (Linn.)

This is an important ornamental herbaceous plant with several bioactive metabolites which may be utilized as potential agents for the development of drugs. Its leaves are utilized for the treatment of wound, bronchitis, diabetes and also having chemo-preventing, antimutagenic, antibacterial and antimicrobial activities.

Wound Healing and Antimicrobial Activity

This plant shows inhibitory action against *Staphylococcus aureus* and *Bacillus subtilis* at dose of 4 and 8 µg/mL (Eldeen *et al.,* 2010). Leaves extracted components of the plant inhibits the growth of *Candida albicans, Aspergillus niger, Micrococcus luteus, Staphylococcus epidermidis*, *Sachharomyces cerevisiae, Staphylococcus aureus Escherichia coli,* and *Pseudomonas aeruginosa* (Vijayasanthi *et al.,* 2011).

Asteraceae

Sonchus asper (Linn.) Hil

S. asper is an herbaceous annual or winter annual; sticky white latex is present in whole plant. This herb contains shoot taproot which is occasionally bushy due to several lateral roots. It has erect stems which are hollow, stout, unbranched or slightly branched measuring 30 to 150 cm tall and most of the time reddish. Several gland-tipped hairs may be present on the up side of stems. This herb contains alternate leaves measuring 4 to 18 cm long and 0.5 to 5 cm wide. Leaves are crisped and many-lobed (5 to 11 lobes on each side) with less number of lobes on upper leaves. It is found in Himalayan region traditionally used as medicine in Pauri Garhwal in Uttarakhand (India). This plant is having various potential bioactive chemical constituents. *S. asper* is used in various human disorders including wounds, burns, gastrointestinal infection, inflammation, cardiac dysfunction, kidney disorders liver disorder, jaundice, cancer along with impotency in humans (Jimoh *et al.,* 2010; Mallik *et al.,* 2014; Purohit & Bohra, 1998).

Wound Healing and Antimicrobial Activity

The methanolic and aqueous leaf extract of *S. asper* possess potent antibacterial activity against *S. aureus* and *B. cereus* whereas *E. coli* inhibited only by methanol extract. Study revealed that the seed extracts possess potent antibacterial activity (Upadhyay *et al.,* 2013). In recent study, Babu, *et al.,* (2019) has successfully synthesized its extract based nanoparticles which gave potential results against *Klebsiella pneumoniae* MTCC 4030, *Staphylococcus aureus MTCC* 1144 and *Escherichia coli* MTCC 40.

Ageratum conyzoides (Linn.)

A. conyzoides measuring 1 m in height and fine white hairs covers both stems and leaves. It has stalked leaves which are ovate measuring 4-10 cm long and 1-5 cm

wide having pointed base with round-toothed margins. This herb contains purple to white flowers measuring less than 6 mm which are arranged in close terminal inflorescences. Its fruits are black in colour which is easily dispersed. The plant commonly grows in ruined and waste areas. *A. conzoides* is utilized traditionally for the treatment of pneumonia, wounds and burns. It is used for quick and effective healing of burn wounds and recommended as anti-rheumatic, anti-dysenteric and antilithic. It is also used to treat fever, rheumatism, headache, colic, arthrosis and also helpful in articulation mobility (Kamboj & Saluja, 2008; Upadhyay, 2011).

Wound Healing and Antimicrobial Activity

A. conyzoides leaves extract possess antibacterial potential against five strains of pathogenic bacteria namely *Escherichia coli, Pseudomonas aeruginosa*, *Staphylococcus aureus, Klebsiella pneumoniae* and *Bacillus subtilis* (Garg and Grewal, 2015).

Saussurea lappa C.B. Clarke

S. lappa is perennial, tall and reaches to the height approximately 1 -2 m with upright stem. Roots of the *S. lappa* are long stout of approximately 60 cm. This herb has membranous leaves which are lobate, stalked and irregularly toothed. The leaves which are present upside are small whereas downside leaves are large with lobately winged stalks. It has stalk less flowers which are deep purple to black arranged in terminal and axillary heads. *S. lappa* is widely distributed in India, Pakistan and China. In India traditionally it may use with the combination of other drugs as well as consumed alone. Mainly roots are utilized for the treatment of asthma, cough and skin diseases (Zahara *et al.,* 2014).

Wound Healing and Antimicrobial Activity

Ethanolic extract of *S. lappa* was screened for the inhibition of acid production, growth and synthesis of water insoluble glucans of *Streptococcus mutans*. Results revealed that its ethanolic extract inhibits growth of test organism as well as the synthesis of glucans (Yu *et al.,* 2007).

Lamiaceae

Leucas indica (Linn.)

L. indica herb is erect and has pubescent branching. It has linear-lanceolate leaves and the flowers are white in colour with four stamens. It used in Garhwal region of Uttarakhand (India) as a wound healer. Leaves are utilized in stomachic, sores and used as sedative. The phytochemicals isolated from the aerial parts of *L. indica* have antioxidant property (Kumar *et al.,* 2011; Sarkar *et al.,* 2013; Babu, *et al.,* 2018).

Wound Healing and Antimicrobial Activity

Antimicrobial activity of crude aerial part extract of plant was studied, its chloroform and methanolic fraction showed positive results against *Escherichia coli, Bacillus subtilis, Salmonella typhi, Staphylococcus aureus* and *Pseudomonas aeruginosa* whereas the aqueous fraction significantly inhibited *Bacillus subtilis, Salmonella typhi and Staphylococcus aureus* (Sarkar *et al.,* 2013).

Ocimum sanctum (Linn.)

O. sanctum has been quoted as "Queen of plants" and the "Mother medicine of nature" because of its large number of medicinal properties (Yamani *et al.,* 2016). Approximately its 13000 species around the world are utilized as drugs. It is heavily branched, erect measuring 3060 cm tall with hairy stems and green sometimes purple leaves having strong essence. Ovate, petiolate leaves measuring up to 5 cm in length and slightly toothed. Its purplish flowers are in elongate racemes in close whorls (Pattanayak *et al.,* 2010). *O. sanctum* is usually prescribed for the treatment of respiratory ailments, diarrhea, skin diseases, malaria, eye diseases, high fever etc. It has also been recommended as anticancer, antifungal, antimicrobial, antidiabetic, remedy for liver and heart disorders etc. (Prakash and Gupta, 2005).

Wound Healing and Antimicrobial Activity

Yamani *et al.,* (2016) reported that *S. aureus* and *E. coli* were completely inhibited by Tulsi oil at the dose of 4.5% and 2.25% although *P. aeruginosa* was partly inhibited. Similarly, Mallikarjun, *et al.,* (2016) tested ethanolic extract of *Ocimum sanctum* at the concentration of 0.5%, 1%, 2%, 5% and 10% against *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans* and *Prevotella intermedia.* Results showed that *Aggregatibacter actinomycetemcomitans* was inhibited at the

concentrations of 5% and 10% whereas *Prevotella intermedia* and *Porphyromonas gingivalis* exhibited resistance.

Aloaceae

Aloe vera (Linn.) Burm

Aloe vera has several synonyms i.e. *A. barbadensis* Mill., *A. perfoliata* L. var., *A. indica* Royle, and *A. vulgaris* Lam. It is a succulent plant having short stem measuring 60–100 cm in length. Its leaves are fleshy and thick which are coloured green to grey-green sometimes with white flecks on upper and lower stem surfaces. The margin of the leaves has jagged edge with small whitish teeth. Its flowers germinate in summer on a spike measuring 90 cm long. The flowers are pendulous having yellow tubular corolla measuring 2-3 cm in length. Aloes has been enormously employed for several disorders more precisely disorders linked with digestion; they have also been utilized for the treatment of skin problems. The term Aloes means the dried juice that flows from the leaves on cutting. It is prescribed for adjuvant therapy along with synthetic drugs and chemotherapy to reduce the drug induced effects. It has been used in various issues such as type II diabetes, eye related problems, enlarged spleen, hepatic disorders, vomiting, respiratory disorders, having laxative properties and helpful for the treatment of in involuntary bowel syndrome (Rajeswari *et al.,* 2012).

Wound Healing and Antimicrobial Activity

Acetone, aqueous and ethanol extracts of *A. vera* possess potent antibacterial activity against *Escherichia coli, Staphylococcus aureus, Streptococcus pyogenes,* and *Pseudomonas aeruginosa* (Arunkumar & Muthuselvam, 2009).

Berberidaceae

Berberis aristata (D.C.)

B. aristata is a spiny herb native to northern Himalayan region. Traditionally it is used in inflammation, skin diseases, menorrhagia, wound healing, diarrhea, jaundice and eye infection (Sharma *et al.,* 2011).

Wound Healing and Antibacterial Activity

The ethanolic root extract of plant shows antifungal activity. It also shows activity against several Gram negative bacteria including *S. typhimurium, S. dysenteriae*, *E. coli and V. cholera* (Shahid *et al.,* 2009).

Periplocaceae

Hemidesmus indicus (Linn.) R. Br.

H. indicus with combination of other drugs is used in snake bites. Its methanolic extract has potential effect against leucorrhoea, bronchitis, chronic rheumatism, syphilis, urinary diseases and lecoderma. Antipyretic and antidiarrheal activities are also reported (Kirtikar & Basu, 1984; Nadkarni *et al.,* 1989).

Wound Healing and Antimicrobial Activity

Extracts from the roots of *H. indicus* inhibit the growth of *S.aureus, K. pneumoniae, P. aeruginosa* (Gayathri & Kannabiran, 2009). In another study by Rajput & Navneet (2019), tested antimicrobial potential of given plant extracts of petroleum ether, methanol, water and ethyl acetate against *Pseudomonas aeruginosa, Staphylococcus aureus, Microsporum audouinii, Malassezia furfur,* and *Candida albicans*. Results reveal that ethyl acetate extract gave best results followed by methanol and petroleum ether.

Rosaceae

Prunus puddum (Roxb.)

P. puddum is traditionally used for the treatment of stone and gravel in the kidney, bleeding disorders, burning sensation and skin diseases (Pallavi *et al.,* 2011).

Wound Healing and Antimicrobial Activity

Antibacterial action of ethanolic extract of *P. puddam* was analyzed with Gram positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative microorganisms (*Salmonella typhi* and *Escherichia coli*). Results showed that it gives positive results against all the tested microorganisms (Sharma, 2013).

Symplocaceae

Symplocos racemosa (Roxb.)

S. racemosa bark is expectorant, astringent, haemostatic, anti-inflammatory, stomachic and suppurative. Traditionally it is used in eye disorders, spongy and bleeding gums, disorders related to the respiratory tract, skin diseases etc. (Kirthikar & Basu, 1999; Nadkarni 1954; Raghunathan & Mitra, 2000.).

Wound Healing and Antimicrobial Activity

Petroleum ether as well as ethanolic extracts were tested against *Enterococcus faecalis, Bacillus cereus, Staphylococcus aureus Klebsiella pneumoniae, Psudomonas aeruginosa* and *E. coli.* Ethanolic extract possesses good antibacterial activity on comparison with petroleum ether (Devmurari, 2010).

Combretaceae

Terminalia chebula (Retz.)

T. chebula is called as the 'King of Medicine' in Tibet. By the name of "Kadukkaai', tribes of Tamil Nadu in India routinely utilizes *T. chebula* as traditional medicine for the treatment of fever, diarrhea, stomach disorders, cough, urinary tract infection, wound infections and skin diseases (Dash, 1991; Rathinamoorthy & Thilagavathi, 2014).

Wound Healing and Antimicrobial Activity

Sato *et al.,* (1997) screened antibacterial efficacy of ethanol extracted fruits of *T. chebula* they found that fruit extract gave considerable antibacterial efficacy against *S. aureus.* They also found that gallic acid and its ethyl ester responsible for this activity. In another study its ethanolic fruit extract showed inhibition against *Salmonella typhi*, *Streptococcus epidermidis* and *Bacillus subtilis* (Kannan *et al.,* 2009).

Meliaceae

Azadirachta indica (A.) Juss

A. indica leaves, bark and seeds shows antibacterial as well as antifungal activities against several pathogens and are also known to exhibit a wide range of pharmacological

properties such as antioxidant, anticarcinogenic, anti-inflammatory, antimalarial, antihyperglycaemic, antiulcer, anti-diabetic properties etc. Due to the presence of several bioactive components its biological activities are accredited. Its aqueous leaves extract has been utilized as a good anti-hyperglycemic agent. Its leaves can be utilized for the several skin related disorders. It can remove toxins from the body and also have free radicals scavenging property (Mohammed & Omer, 2015).

Wound Healing and Antimicrobial Activity

Mohammed & Omer (2015) reported that ethanolic leaves extract of *A. indica* exhibit potential antibacterial activity against *K. pneumoniae, P. mirabilis, E. coli, S. aureus and E. faecalis* at all concentrations used. Huge number of research has been conducted on several plants to know whether they are helpful or not in the treatment of wound infection. Some of the experimentally evidenced plants are enlisted in the table 1.

CONCLUSION

In India usage of medicinally important plants for restorative purposes has been archived dated back in Ayurveda since they are fundamental for the survival of mankind. A noteworthy extent of populace for the most part having a place with provincial territories is still reliant on conventional arrangement of prescriptions for their different wellbeing needs. There are huge list of plants which have been accounted for their injury recuperating properties because of quality of significant phyto-constituents. The mixture of traditional and present day information can deliver better medications for several infections with fewer side effects. Such kind of conventional information on plant can shape a reason for clinical, therapeutic, pharmacological and novel medication conveyance framework for wound healing items. Lots of data is recorded with plants local name, scientific name with family and part used for the treatment. These data must be tested for their adequacy.

Table 1. Experimentally evidenced plants used for the treatment for wound infection

S. No.	Plant	Common name	Family	Part used	Extract	Reference
1	*Acalypha indica* L.	Indian Copperleaf	Euphorbiaceae	Leaves	Ethanol	Ganeshkumar *et al*., (2012)
2	*Acanthus polystachyus* L.	Bear's breeches	Acanthaceae	Leaves	Methanol	Demilew *et al*., (2018)
3	*Acorus calamus* L.	Sweet flag	Acoraceae	Leaves	Ethanol	Jain *et al*., (2010)
4	*Allium sativum* L.	Garlic	Liliaceae	Bulb	Ethanol	Zuber *et al*., (2013)
5	*Adhatoda vasica* L.	Chu Mue	Acanthaceae	Leaves	Methanol	Vinothapooshan & Sundar, (2010)
6	*Alternanthera brasiliana* L.	Brazilian joyweed	Amaranthaceae	Leaves	Methanol	Barua *et al.,* (2009)
7	*Andrographis paniculata* Burm.	Indian Echinacea	Acanthaceae	Whole plant	Petroleum ether, Ethanol	Mohanty *et al*., (2010)
8	*Areca catechu* L.	Arecanut, Betel nut	Palmaceae	Nut	Ethanol	Rani *et al*., (2018)
9	*Asparagus racemosus* Willd.	Satavar	Asparagaceae	Roots	Water	Kodancha *et al*., (2011)
10	*Acacia catechu* L.	Cutch tree	Fabaceae	Bark	water, Ethanol	Reddy *et al.,* (2011)
11	*Achyranthes aspera* L.	Apamarga	Amaranthaceae	Leaves	Methanol	Barua *et al.,* (2012)
12	*Agrimonia pilosa* Ledeb.	Belur	Rosaceae	whole plant	-	Chopda & Mahajan, (2009)
13	*Alstonia scholaris* L. R. Br.	Saptparni	Apocynaceae	Leaves	Ethanol, Water	Arulmozhi *et al.,* (2007)
14	*Butea monosperma* Lam.	Palash	Papilionaceae	Bark	Ethanol	Sumitra *et al.,* (2005)
15	*Betula alnoides* Buch.-Ham.	In Birch	Betulaceae	Stem	-	Chopda & Mahajan, (2009)
16	*Balanites roxburghii* Planch	Hingana	Simaronbaceae	Stem	-	Chopda & Mahajan, (2009)
17	*Berberis aristata* D.C.	Daruhalad	Berberidaceae	Stem	-	Chopda & Mahajan, (2009)
18	*Calotropis gigantea* R.Br	Milkweed	Asclepiadaceae	Roots bark	Petroleum ether, Ethanol	Deshmukh *et al., (2009)*
19	*Carica papaya* L.	Papaya	Caricaceae	Seeds	Ethanol	Nayak *et al.,* (2012)
20	*Cassia fistula* L.	Amaltas	Leguminosae	Leaves	Ethanol	Kumar *et al*.,(2006)
21	*Catharanthus roseus* L.	Sadabahar	Apocyanaceae	Flowers	Ethanol	Nayak & Pereira, (2006)
22	*Cordia dichotoma* Forst.	Lasora	Boraginaceae	Fruit	Ethanol	Kuppast & Nayak (2005)
23	*Centella asiatica* L.	Asiatic pennywort	Apiaceae	Aerial parts	n Hexane, Methanol, Ethyl acetate, Water	Somboonwong *et al*., (2012)
24	*Calotropis procera* L.	Aak	Apocynaceae	Latex	Chloroform, Water	Rasik *et al.,* (1999)
25	*Cassia alata* L.	Candle bush	Fabaceae	Leaves	Methanol	Kanedi *et al.,* (2016)
26	*Calendula officinalis* L.	Parigold	Asteraceae	Flowers	Ethanol	Parente *et al*., (2011)
27	*Cassia auriculata* L.	Avaram	Caesalpiniaceae	Flowers	Ethanol	Vaidyanathan *et al*., (2014)
28	*Cleome viscose* L.	Dog mustard	Cleomaceae	Whole plant	Methanol	Panduraju *et al.*, (2011)
29	*Curcuma longa* L.	Turmeric	Zingiberaceae	Rhizomes	Ethanol	Miah *et al*., (2017)
30	*Desmodium triquetrum* DC.	Balolia	Fabaceae	Leaves	Ethanol	Shirwaikar *et al.,* (2003)
31	*Datura stramonium* L.	Dhatura	Solanaceae	Leaves	-	Chopda & Mahajan, (2009)
32	*Dendrophthoe falcata* L.	Banda	Loranthaceae	Aerial parts	Ethanol	Pattanayak & Sunita, (2008)
33	*Dodonea viscose* L.	Vilayti-mehdi	Sapindaceae	Whole plant	Methanol	Ramya *et al.,* (2011)
34	*Embelia ribes* Burm.	Bashmak	Myrsinaceae	Leaves	Ethanol	Swamy *et al.,* (2007)
35	*Eupatorium odoratum* L.	Siam weed	Asteraceae	Leaves	Water	Biswal *et al.,* (1997)
36	*Euphorbia hirta* L.	Barokhervi	Euphorbiaceae	Leaves	Ethanol	Tuhin *et al.,* (2017)
37	*Ficus benghalensis* F.	Bargad	Moraceae	Bark	Ethanol, Water	Garg & Paliwal, (2011)
38	*Ficus religiosa* L.	Peepal	Moraceae	Leaves	Water	Chowdhary *et al.*, (2014)
39	*Gymnema sylvestre* R.Br.	Australian cowplan	Apocynaceae	Leaves	Ethanol	Malik *et al.,* (2009)
40	*Glycyrrhiza glabra* L.	Mulhati	Fabaceae	Roots	Water	Chakravarthi & Avadhani, (2013)
41	*Heliotropium indicum* L.	Indian heliotrope	Boraginaceae	Leaves	Methanol	Dash & Murthy, (2011)
42	*Indigofera enneaphylla* L.	Birdsville indigo	Fabaceae	Whole plant	Ethanol	Sivagamy *et al.,* (2012)
43	*Jasminum grandiflorum* L.	Jasmin	Oleaceae	Leaves	Ethanol	Mishra *et al.,* (2010)
44	*Kaempferia galanga* L.	Chandramula	Zingiberaceae	Rhizomes	Alcoholic	Shanbhag *et al.*, (2006)
45	*Lycopodium serratum* Thunb.	Club moss	Lycopodiaceae	Whole plant	Ethanol, Water	Manjunatha *et al.*, (2007)
46	*Mimosa pudica* L.	Lajjalu	Mimosaceae		Methanol/Water	Kokane *et al.,* (2009)
47	*Mimusops elengi* L.	Bakul	Sapotaceae	Leaves	Methanol	Singh *et al.,* (2016)
48	*Michelia Champaca* L.	Champak	Magnoliaceae	whole plant	Alcoholic	Dwajani & Shanbhag, (2008)
49	*Mirabilis jalapa* L.	Four o'clock flower	Nyctaginaceae	Roots	Hydro-methanolic	Gogoi *et al.,* (2013)
50	*Piper betel* L.	Betel Vine	Piperaceae	Leaves	Water	Ghazali *et al.,* (2016)

REFERENCES

Arulmozhi, S., Rasal, V. P., Sathiyanarayanan, L., & Purnima, A. (2007). *Screening of* Alstonia scholaris *Linn. R. Br., for wound healing activity*. Academic Press.

Arunkumar, S., & Muthuselvam, M. (2009). Analysis of phytochemical constituents and antimicrobial activities of *Aloe vera* L. against clinical pathogens. *World Journal of Agricultural Sciences*, *5*(5), 572–576.

Babu, N., Akash, Singh, A., & Navneet. (2018). Therapeutics potential and pharmacological properties of *Leucas indica*: A review. *The Pharma Innovation*, *7*(7), 564–568.

Babu, N., Pathak, V. M., & Singh, A. & Navneet. (2019). *Sonchus asper* leaves aqueous extract mediated synthesis of Titanium dioxide nanoparticles. *The Pharma Innovation*, *8*(4), 817–822.

Babu, N., Singh, A., Singh, R., & Navneet. (2017). A review on therapeutic potential and phytochemistry of *Tephrosia purpurea. Bulletin of Pure & Applied Sciences-Botany*, *36*(2), 91–104. doi:10.5958/2320-3196.2017.00013.1

Barua, C. C., Talukdar, A., Begum, S. A., Pathak, D. C., Sarma, D. K., Borah, R. S., & Gupta, A. (2012). In vivo wound-healing efficacy and antioxidant activity of *Achyranthes aspera* in experimental burns. *Pharmaceutical Biology*, *50*(7), 892–899. doi:10.3109/13880209.2011.642885 PMID:22480137

Barua, C. C., Talukdar, A., Begum, S. A., Sarma, D. K., Pathak, D. C., Barua, A. G., & Bora, R. S. (2009). Wound healing activity of methanolic extract of leaves of *Alternanthera brasiliana* Kuntz using in vivo and in vitro model. *Indian Journal of Experimental Biology*, *47*, 1001–1005. PMID:20329705

Biswal, P. R., Sardar, K. K., Parija, S. C., Mishra, P. R., & Misra, S. N. (1997). Wound healing effect of *Eupatorium odoratum* Linn. and Himax in rabbits. *Indian Journal of Indigenous Medicines*, *19*(1), 71–74.

Carville, K. (2008). Principles of best practice: Wound infection in clinical practice. An international consensus. World Union of Wound Healing Societies, 1-12.

Chakravarthi, K. K., & Avadhani, R. (2013). Beneficial effect of aqueous root extract of *Glycyrrhiza glabra* on learning and memory using different behavioral models: An experimental study. *Journal of Natural Science, Biology, and Medicine*, *4*(2), 420–425. doi:10.4103/0976-9668.117025 PMID:24082744

Chattopadhyay, R. R., Bhattacharyya, S. K., Medda, C., Chanda, S., Datta, S., & Pal, N. K. (2007). Antibacterial activity of black myrobalan (Fruit of *Terminalia chebula* Retz.) against uropathogen *Escherichia coli. Phcog. Rev*, *3*(11), 212–215.

Chopda, M. Z., & Mahajan, R. T. (2009). Wound healing plants of Jalgaon district of Maharashtra state, India. *Ethnobotanical Leaflets*, *13*, 1–32.

Chowdhary, N., Kaur, M., Singh, A., & Kumar, B. (2014). Wound healing activity of aqueous extracts of *Ficus religiosa* and *Ficus benghalensis* leaves in rats. *Indian Journal of Research in Pharmacy and Biotechnology*, *2*(2), 1071–1081.

Damle, M. (2014). *Glycyrrhiza glabra* (Liquorice) potent medicinal herb. *Indian Journal of Herbal Medicine*, *2*(2), 132–136.

Dash, B. (1991). *Materia Medica of Ayurveda* (Vol. B). New Delhi: Jain Publishers.

Dash, G. K., & Murthy, P. N. (2011). Studies on wound healing activity of *Heliotropium indicum* Linn. leaves on rats. *ISRN Pharmacology*, *2011*, 1–8. doi:10.5402/2011/847980 PMID:22084720

Demilew, W., Adinew, G. M., & Asrade, S. (2018). Evaluation of the wound healing activity of the crude extract of leaves of *Acanthus polystachyus* Delile (Acanthaceae). *Evidence-Based Complementary and Alternative Medicine*, *2018*, 1–9. doi:10.1155/2018/2047896 PMID:29991951

Deshmukh, P. T., Fernandes, J., Atul, A., & Toppo, E. (2009). Wound healing activity of *Calotropis gigantea* root bark in rats. *Journal of Ethnopharmacology*, *125*(1), 178–181. doi:10.1016/j.jep.2009.06.007 PMID:19539020

Deshpande, S. S., Shah, G. B., & Parmar, N. S. (2003). Antiulcer activity of *Tephrosia purpurea* in rats. Ind. *Journal of Pharmaceutics*, *35*, 168–172.

Devmurari, V. P. (2010). Phytochemical screening study and antibacterial evaluation of *Symplocos racemosa* Roxb. *Archives of Applied Science Research*, *2*(1), 354–359.

Dwajani, S., & Shanbhag, T. (2008). *Michelia champaca*: Wound healing activity in immunosuppressed rats. *The Internet Journal of Alternative Medicine*, *7*(2), 1–5.

Dwivedi, D., Dwivedi, M., Malviya, S., & Singh, V. (2017). Evaluation of wound healing, antimicrobial and antioxidant potential of *Pongamia pinnata* wistar rats. *J of Trad and Comp Med*, *7*(1), 79–85. PMID:28053891

Eldeen, I. M. S., Van Heerden, F. R., & Van Staden, J. (2010). *In vitro* biological activities of niloticane, a new bioactive cassane diterpene from the bark of *Acacia nilotica* subsp. kraussiana. *Journal of Ethnopharmacology*, *128*(3), 555–560. doi:10.1016/j.jep.2010.01.057 PMID:20138134

Ganeshkumar, M., Ponrasu, T., Krithika, R., Iyappan, K., Gayathri, V. S., & Suguna, L. (2012). Topical application of *Acalypha indica* accelerates rat cutaneous wound healing by up-regulating the expression of Type I and III collagen. *Journal of Ethnopharmacology*, *142*(1), 14–22. doi:10.1016/j.jep.2012.04.005 PMID:22521732

Garg, P., & Grewal, A. (2015). In vitro antibacterial activity of *Ageratum conyzoides* L. *World Journal of Pharmacy and Pharmaceutical Sciences*, *4*(7), 893–897.

Garg, V. K., & Paliwal, S. K. (2011). Wound-healing activity of ethanolic and aqueous extracts of *Ficus benghalensis. Journal of Advanced Pharmaceutical Technology & Research*, *2*(2), 110–114. doi:10.4103/2231-4040.82957 PMID:22171302

Gayathri, M., & Kannabiran, K. (2009). Antimicrobial activity of *Hemidesmus indicus, Ficus bengalensis* and *Pterocarpus marsupium* roxb. *Indian Journal of Pharmaceutical Sciences*, *71*(5), 578–581. doi:10.4103/0250-474X.58182 PMID:20502584

Ghazali, N. A., Elmy, A., Yuen, L. C., Sani, N. Z., Das, S., Suhaimi, F., & Thent, Z. C. (2016). *Piper betel* leaves induces wound healing activity via proliferation of fibroblasts and reducing 11β hydroxysteriod dehydrogenase-1 expression in diabetic rat. *Journal of Ayurveda and Integrative Medicine*, *7*(4), 198–208. doi:10.1016/j.jaim.2016.08.008 PMID:27889427

Gogoi, J., Nakhuru, K. S., Chattophadhayay, P., Rai, A. K., Gogoi, H. K., & Veer, V. (2013). In vivo evaluation of cutaneous wound healing activity of *Mirabilis jalapa* L radix. *Oriental Pharmacy and Experimental Medicine*, *14*(2), 103–109. doi:10.100713596-013-0122-6

Halder, P. K., Paul, N., & Beg, M. R. A. (2014). Prospect of *Pongamia pinnata* (Karanja) in Bangladesh: A sustainable source of liquid fuel. *Journal of Renewable Energy*, *2014*, 1–13. doi:10.1155/2014/647324

Hojo, H., & Sato, J. (2002). Antifungal activity of Licorice (*Glycyrrhiza glabra)* and potential applications in beverage foods. *J Food Ingr Japan*, *203*, 45–49.

Jain, N., Jain, R., Jain, A., Jain, D. K., & Chandel, H. S. (2010). Evaluation of wound-healing activity of *Acorus calamus* Linn. *Natural Product Research*, *24*(6), 534–541. doi:10.1080/14786410802531782 PMID:20182947

Jimoh, F. O., Adedapo, A. A., & Afolayan, A. J. (2010). Comparison of the nutritive value, antioxidant and antibacterial activities of *Sonchus asper* and *Sonchus oleraceus. Chem. Globe Pub*, *5*(1), 29–42.

Kamboj, A., & Saluja, A. K. (2008). *Ageratum conyzoides* L.: A review on its phytochemical and pharmacological profile. *Inter J of Green Pharma*, *2*(2), 59–68. doi:10.4103/0973-8258.41171

Kanedi, M., Rokiban, A., & Widodo, S., Nopiyansah, I., & Fauziah, L. (2016). Healing effect of leaf extract of candlebush (*Cassia alata* L.) on cutaneous wound infected with *Trichophyton rubrum. World Journal of Pharmaceutical and Life Sciences*, *2*(5), 42–50.

Kanitakis, J. (2002). Anatomy, histology and immunohistochemistry of normal human skin. *European Journal of Dermatology*, *12*(4), 390–401. PMID:12095893

Kannan, P., Ramadevi, S. R., & Hopper, W. (2009). Antibacterial activity of *Terminalia chebula* fruit extract. *African Journal of Microbiological Research*, *3*(4), 180–184.

Kaufman, T., Kalderon, N., Ullmann, Y., & Berger, J. (1988). *Aloe vera* gel hindered wound healing of experimental second degree burns. *The Journal of Burn Care & Rehabilitation*, *9*(2), 156–159. doi:10.1097/00004630-198803000-00005 PMID:3360818

Kirthikar, K. R., & Basu, B. D. (1999). *Indian medicinal plants* (2nd ed.). Popular Publication.

Kirtikar, K. R., & Basu, B. D. (1984). Indian medicinal plants. Delhi: Periodical Expert Agency.

Kodancha, P., Kumar, S., Rajput, R., Patil, V., Udupa, A. L., Gupta, S., ... Shubha, H. V. (2011). Wound healing profile of *Asparagus racemosus* (Liliaceae) wild. *Current Pharma Research*, *1*(2), 111–114. doi:10.33786/JCPR.2011.v01i02.004

Kokane, D. D., More, R. Y., Kale, M. B., Nehete, M. N., Mehendale, P. C., & Gadgoli, C. H. (2009). Evaluation of wound healing activity of root of *Mimosa pudica. Journal of Ethnopharmacology*, *124*(2), 311–315. doi:10.1016/j.jep.2009.04.038 PMID:19397984

Kumar, M., Bussmann, R. W., Joshi, M., & Kumar, P. (2011). Ethnomedicinal uses of plants close to rural habitation in Garhwal Himalaya, India. *Journal of Medicinal Plants Research*, *5*(11), 2252–2260.

Kumar, M. S., Sripriya, R., Raghavan, H. V., & Sehgal, P. K. (2006). Wound healing potential of *Cassia fistula* on infected albino rat model. *The Journal of Surgical Research*, *131*(2), 283–289. doi:10.1016/j.jss.2005.08.025 PMID:16242721

Kuppast, I. J., & Nayak, P. V. (2005). Wound healing activity of *Cordia dichotoma* Forst. f. fruits. *Research article, 5*(2), 99-102.

Laishram, A., Naik, J., Reddy, S., & Jayasimha Rayalu, D. (2013). Phytochemical analysis, TLC profiling and antimicrobial activity of *Tephrosia purpurea*. *International Journal of Pharmacy & Life Sciences*, *4*(2), 2375–2379.

Malik, J. K., Manvi, F. V., Nanjware, B. R., & Sanjiv, S. (2009). Wound healing properties of alcoholic extract of *Gymnema sylvestre* R. Br. leaves in rats. *Journal of Pharmacy Research*, *2*(6), 1029–1030.

Mallik, P., Mishra, S. K., & Satapathy, K. B. (2014). Studies on the antibacterial and antioxidant activities of *Sonchus asper* (L.) Hill and *Seseli diffusum* (Roxb. Ex sm.) Sant. & Wagh. *ISOR J. Pharma. Bio. Sci*, *9*(6), 24–27. doi:10.9790/3008-09642427

Mallikarjun, S., Rao, A., Rajesh, G., Shenoy, R., & Pai, M. (2016). Antimicrobial efficacy of Tulsi leaf (*Ocimum sanctum*) extract on periodontal pathogens: An in vitro study. *Journal of Indian Society of Periodontology*, *20*(2), 145–150. PMID:27143825

Manjunatha, B. K., Krishna, V., Vidya, S. M., Mankani, K. L., & Manohara, Y. N. (2007). Wound healing activity of *Lycopodium serratum. Indian Journal of Pharmaceutical Sciences*, *69*(2), 283–287. doi:10.4103/0250-474X.33159

Miah, M. A. H., Hasan, M., Sarker, Y. A., Alam, M. M., & Juyena, N. S. (2017). Clinical evaluation of ethanolic extract of curcumin (*Curcuma longa*) on wound healing in Black Bengal goats. *Journal of Advanced Veterinary and Animal Research*, *4*(2), 181–186. doi:10.5455/javar.2017.d209

Mishra, S. B., Mukerjee, A., & Vijayakumar, M. (2010). Wound healing activity of the aqueous alcoholic extract of *Jasminum grandiflorum* Linn leaves. *Pharmacologyonline*, *3*, 35–40.

Moffatt, C. J. (2005). Identifying criteria for wound infection. European Wound Management Association.

Mohammed, H. A., & Omer, A. F. A. (2015). Antibacterial activity of *Azadirachta indica* (Neem) leaf extract against bacterial pathogens in Sudan. *American Journal of Research Communication*, *3*(5), 246–251.

Mohanty, A., Pradhan, D. K., Mishra, M. R., Sahoo, J. K., Mishra, A., Nandy, B. C., & Mokade, L. (2010). Preliminary pytochemical screening and wound healing activity of *Andrographis peniculata. Journal of Chemical and Pharmaceutical Research*, *2*(4), 649–654.

Nadkarni, A. N. (1989). *Hemidesmus indicus* R. *Br. Doctor KM Nadkarni's Indian Materia Medica*, *1*, 619–622.

Nadkarni, K. M. 1954. *Indian materia Medica.* Popular Prakashan.

Nayak, B. S., & Pereira, L. M. P. (2006). *Catharanthus roseus* flower extract has wound-healing activity in Sprague Dawley rats. *BMC Complementary and Alternative Medicine*, *6*(4), 1–6. doi:10.1186/1472-6882-6-41 PMID:17184528

Nayak, B. S., Ramdeen, R., Adogwa, A., Ramsubhag, A., & Marshall, J. R. (2012). Wound-healing potential of an ethanol extract of *Carica papaya* (Caricaceae) seeds. *International Wound Journal*, *9*(6), 650–655. doi:10.1111/j.1742-481X.2011.00933.x PMID:22296524

Pallavi, G., Gupta, V., & Rishi, R. (2011). Ethnopharmaco–botanical review of padmaka–prunus puddum roxb. *International Journal of Ayurvedic And Herbal Medicine*, *1*(3), 87–99.

Panduraju, T., Parvathi, B., Rammohan, M., & Reddy, C. S. (2011). Wound healing properties of *Cleome viscosa* Linn. *Hygeia JD Med*, *3*(1), 41–45.

Parente, L. M. L., Júnior, L., de Souza, R., Tresvenzol, L. M. F., Vinaud, M. C., de Paula, J. R., & Paulo, N. M. (2011). Wound healing and anti-inflammatory effect in animal models of *Calendula officinalis* L. growing in Brazil. *Evidence-Based Complementary and Alternative Medicine*, 1–7. PMID:22315631

Pattanayak, P., Behra, P., Das, D., & Panda, S. K. (2010). *Ocimum sanctum* Linn. A reservoir plant for therapeutic applications:An overview. *Pharmacognosy Reviews*, *4*(7), 95–105. doi:10.4103/0973-7847.65323 PMID:22228948

Pattanayak, S. P., & Sunita, P. (2008). Wound healing, anti-microbial and antioxidant potential of *Dendrophthoe falcata* (Lf) Ettingsh. *Journal of Ethnopharmacology*, *120*(2), 241–247. doi:10.1016/j.jep.2008.08.019 PMID:18790035

Prakash, P., & Gupta, N. (2005). Therapeutic uses of *Ocimum sanctum* Linn (Tulsi) with a note on eugenol and its pharmacological actions: A short review. *Indian Journal of Physiology and Pharmacology*, *49*(2), 125–131. PMID:16170979

Purohit, P., & Bohra, A. (1998). Effect of some plants extracts on conidial germination of some important phytopathogenic fungi. *Geobios*, *17*, 183–184.

Raghunathan, K., & Mitra, M. K. (2000). *Pharmacognosy of indigenous drugs*. New Delhi, India: Central Council of Research in Ayurveda and Siddhs.

Rajeswari, R., Umadevi, M., Rahale, C. S., Pushpa, R., Selvavenkadesh, S., & Kumar, K. P. S. D., & Bhowmik, D. (2012). *Aloe vera:* The miracle plant its medicinal and traditional uses in India. *Journal of Pharmacognosy and Phytochemistry*, *1*(4), 118–124.

Rajput, M., & Navneet. (2019). Antimicrobial potential of *Hydnocarpus laurifolia* seeds utilized in folkloric medicine: A possible alternative in the treatment of scalp infections. *The Pharma Innovation Journal*, *8*(1), 1–5.

Ramya, R., Anudeepa, J., Senthilkumar, C., Rajendran, S. S., Sivasakthi, R., Moorthy, C., & Venkatnarayanan, D. R. (2011). Wound healing activity of *Dodonea viscosa* Linn ointment in rats. *International Journal of Research in Pharmacy and Chemistry*, *1*(3), 481–483.

Rangama, B. N. L. D., Abayasekara, C. L., Panagoda, G. J., & Senanayake, M. R. D. M. (2009). Antimicrobial activity of *Tephrosia purpurea* (Linn.) Pers. and *Mimusops elengi* (Linn.) against some clinical bacterial isolates. *J. Natn. Sci. Found. Sri Lan*, *37*(2), 139–145. doi:10.4038/jnsfsr.v37i2.1071

Rani, S., Rahman, K., & Idris, M. (2018). Ethnomedicinal, pharmacological and phytochemical screening of supari (*Areca catechu* Linn.): A review. *Research & Reviews*. *Journal de Pharmacologie*, *8*(1), 6–20.

Rasik, A. M., Raghubir, R., Gupta, A., Shukla, A., Dubey, M. P., Srivastava, S., & Kulshrestha, D. K. (1999). Healing potential of *Calotropis procera* on dermal wounds in Guinea pigs. *Journal of Ethnopharmacology*, *68*(1), 261–266. doi:10.1016/S0378-8741(99)00118-X PMID:10624886

Rathinamoorthy, R., & Thilagavathi, G. (2014). *Terminalia chebula*-Review on Pharmacological and Biochemical Studies. *International Journal of Pharm Tech Research*, *6*(1), 97–116.

Reddy, B. K., Gowda, S., & Arora, A. K. (2011). Study of wound healing activity of aqueous and alcoholic bark extracts of *Acacia catechu* on rats. *Journal of Pharmaceutical Sciences*, *1*(3), 220–225.

Rodriguez, B. M., Cruz, N. I., & Suarez, A. (1988). Comparative evaluation of *Aloe vera* in management of burn wounds in guinea pigs. *Plastic and Reconstructive Surgery*, *81*(3), 386–389. doi:10.1097/00006534-198803000-00012 PMID:3340673

Sarkar, M., Das, G., Pathak, S. K., Maitra, S., & Samanta, A. (2013). Evaluation of in vivo wound healing and in vitro antibacterial activities of the different extract of *Leucas indica* Linn. *International Journal of Pharmacy and Pharmaceutical Sciences*, *5*(3), 333–340.

Sato, Y., Oketani, H., Singyouchi, K., Ohtsubo, T., Kihara, M., Shibata, H., & Higuti, T. (1997). Extraction and purification of effective antimicrobial constituents of *Terminalia chebula* Rets. against methicillin-resistant *Staphylococcus aureus. Biological & Pharmaceutical Bulletin*, *20*(4), 401–404. doi:10.1248/bpb.20.401 PMID:9145218

Shahid, M., Rhaim, T., & Shahzad, A., Tajuddin, Latif, A., Fatma, T., … Mustafa, S. (2009). Ethnobotanical studies on *Berberis aristata* D.C. root extract. *African Journal of Biotechnology*, *8*(40), 556–563.

Shanbhag, T. V., Sharma, C., Adiga, S., Bairy, K. L., Shenoy, S., & Shenoy, G. (2006). Wound healing activity of alcoholic extract of *Kaempferia galanga* in Wistar rats. *Indian Journal of Physiology and Pharmacology*, *50*(4), 384–390. PMID:17402268

Sharma, B. C. (2013). In vitro antibacterial activity of certain folk medicinal plants from Darjeeling Himalayas used to treat microbial infections. *Journal of Pharmacognosy and Phytochemistry*, *2*(4), 1–4.

Sharma, K., Bairwa, R., Chauhan, N., Shrivastava, B., & Saini, N. K. (2011). Beberis aristata [review]. *International Journal of Research and Analytical Review*, *2*(2), 383–388.

Shirwaikar, A., Jahagirdar, S., & Udupa, A. L. (2003). Wound healing activity of *Desmodium triquetrum* leaves. *Indian Journal of Pharmaceutical Sciences*, *65*(5), 461–464.

Singh, N., Dixit, V., Irchhaiya, R., & Alok, S. (2016). Wound healing activity of *Mimusops elengi* Linn. *International Journal of Pharmaceutical Sciences and Research*, *7*(1), 349–352.

Sivagamy, M., Jeganathan, M. R., Manavalan, R., & Senthamarai, R. (2012). Wound healing activity of *Indigofera enneaphylla* Linn. *Int J Adv Pharm Chem Biol*, *1*(2), 211–214.

Somboonwong, J., Kankaisre, M., Tantisira, B., & Tantisira, M. H. (2012). Wound healing activities of different extracts of *Centella asiatica* in incision and burn wound models: An experimental animal study. *BMC Complementary and Alternative Medicine*, *12*(1), 103. doi:10.1186/1472-6882-12-103 PMID:22817824

Sumitra, M., Manikandan, P., & Suguna, L. (2005). Efficacy of *Butea monosperma* on dermal wound healing in rats. *The International Journal of Biochemistry & Cell Biology*, *37*(3), 566–573. doi:10.1016/j.biocel.2004.08.003 PMID:15618014

Swamy, H. K., Krishna, V., Shankarmurthy, K., Rahiman, B. A., Mankani, K. L., Mahadevan, K. M., ... Naika, H. R. (2007). Wound healing activity of embelin isolated from the ethanol extract of leaves of *Embelia ribes* Burm. *Journal of Ethnopharmacology*, *109*(3), 529–534. doi:10.1016/j.jep.2006.09.003 PMID:17034970

Tuhin, R. H., Begum, M. M., Rahman, M. S., Karim, R., Begum, T., Ahmed, S. U., & Begum, R. (2017). Wound healing effect of *Euphorbia hirta* Linn. (Euphorbiaceae) in alloxan induced diabetic rats. *BMC Complementary and Alternative Medicine*, *17*(1), 423. doi:10.118612906-017-1930-x PMID:28836990

Upadhyay, H., Kumar, A., Gupta, M. K., Sharma, A., & Rahal, A. (2013). Validation of medicinal values of traditionally used *Sonchus asper* (prickly sow thistle) leaves for the treatment of skin ailments. *Advan. Med. Plant Res*, *1*(1), 29–35.

Upadhyay, R. K. (2011). Plant natural products: Their pharmaceutical potential against disease and drug resistant microbial pathogens. *Journal of Pharmacy Research*, *4*(4), 1179–1185.

Vaidyanathan, L., Thanikachalam, D., & Sivaswamy, L. T. (2014). Evaluation of wound healing potency of *Cassia auriculata* flower extracts using chick embryo wound model. *International Journal of Pharmaceutical Sciences Review and Research*, *27*(2), 222–227.

Vijayasanthi, M., Kannan, V., Venkataswamy, R., & Doss, A. (2011). Evaluation of the antibacterial Potential of various solvent extracts of *Acacia nilotica* linn. leaves. *J. Drug Med*, *4*(1), 91–96.

Vinothapooshan, G., & Sundar, K. (2010). Wound healing effect of various extracts of *Adhatoda vasica*. *International Journal of Pharma and Bio Sciences*, *1*(4), 530–536.

Yamani, H. A., Pang, E. C., Mantri, N., & Deighton, M. A. (2016). Antimicrobial activity of Tulsi (*Ocimum tenuiflorum*) essential oil and their major constituents against three species of bacteria. *Frontiers in Microbiology*, *7*, 1–10. doi:10.3389/fmicb.2016.00681 PMID:27242708

Yu, H. H., Lee, J. S., Lee, K. H., Kim, K. Y., & You, Y. O. (2007). *Saussurea lappa* inhibits the growth, acid production, adhesion and water insoluble glucan synthesis of *Streptococcus mutans*. *Journal of Ethnopharmacology*, *111*(2), 413–417. doi:10.1016/j.jep.2006.12.008 PMID:17234374

Zadeh, J. G., Kor, Z. M., & Goftar, M. K. (2013). Licorice (*Glycyrrhiza glabra* Linn) as a valuable medicinal plant. *International Journal of Advanced Biological and Biomedical Research*, *1*(10), 1281–1288.

Zahara, K., Tabassum, S., Sabir, S., Arshad, M., Rahematullah, Q., Amjad, S. M., & Chaudhari, K. S. (2014). A review of therapeutic potential of *Saussurea lappa*- an endangered plant from Himalaya. *Asian Pacific Journal of Tropical Medicine*, *7*(1), 61–69. doi:10.1016/S1995-7645(14)60204-2 PMID:25312191

Zuber, M., Rajesh, V., Anusha, K., Reddy, C. R., & Tirupathi, A. (2013). Wound healing activity of ethanolic extract of *Allium sativum* on alloxan induced diabetic rats family (Liliaceae). *International Journal of Science Inventions Today*, *2*(1), 40–57.

Chapter 10
Herbal Bioactives:
An Escape to ESKAPE Pathogens

Surbhi Mundra
Central Drug Research Institute, India

Padam Singh
https://orcid.org/0000-0002-8844-9157
Translational Health Science and Technology, India

ABSTRACT

Infection is caused in the human body due to the invasion of pathogenic microbes, their multiplication, and production of toxins. The ESKAPE pathogen comprises a group of six bacterial pathogens, namely Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp. These pathogens are associated with the emerging cases of antimicrobial resistance to commonly used antibiotics such as penicillin, vancomycin, etc. Most of these pathogens are multidrug resistant, which is among the major threats to human health at present. The developing resistance to existing antibiotics imposes a burden on modern science to exercise the mechanism behind this and also the identification of novel targets to combat antimicrobial resistance. This chapter describes briefly about the mechanism of development of antimicrobial resistance and some herbal medications that can be used to combat the same. It also describes some of the traditional preventives that can be practiced to deal with infections.

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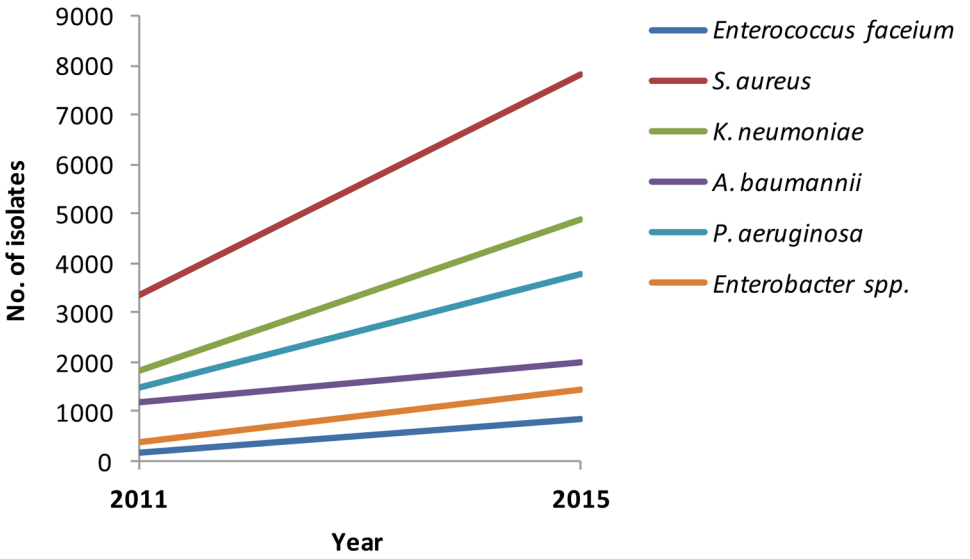
INTRODUCTION

Nosocomial infections are caused by a variety of microbes, including viruses, fungi, bacteria, and many other agents. These infectious pathogens can be born inside the host, i.e., endogenous or may be transferred from an external source, i.e., exogenous. There are increasing incidences of antibiotic resistance in such pathogens leading to a significant burden on the healthcare system and affecting the mortality and morbidity rates. There is a group of six bacterial pathogens, called the ESKAPE pathogens, which comprises *of Enterococcus faecium, Streptococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp. These bacterial pathogens are grouped differently by the Infectious Disease Society of America due to emerging cases of antibiotic resistance among them or simply because of their ability to escape the effect of antibiotics (WHO, 2017). This emerging resistance mechanism in these species poses a great threat to life on earth and on the other hand, demands a novel and active approach to target the bacterial infections.

MDR infections are among the top three causes of threat to public health. In the year 2017, the World Health Organization (WHO) developed a global pathogen priority list (PPL), for the antibiotic-resistant bacteria to stimulate research and healthcare initiatives. The bacterial strains from ESKAPE pathogens top the list of PPL. The global PPL has divided bacterial pathogens into three priority tiers based on their abundance, emergence, and significance as critical, high, and medium (Rice, 2010). The bacteria in the ESKAPE pathogens list are among the critical and high tier. Carbapenem-resistant *A. baumannii* and *P. aeruginosa* along with extended spectrum β-lactamases (ESBL) or carbapenem-resistant *K. peumoniae* and *Enterobacter* spp. are listed in the critical priority list of pathogens, whereas vancomycin resistant *E. faecium* (VRE) and vancomycin and methicillin-resistant *S. aureus* (VRSA and MRSA) are in the list of high priority group. So, it needs special attention to compensate for the elevating mortality and morbidity rates (Llaca-Diaz, 2012). A survey of clinical samples from South Africa, over five years from the year 2011 to 2015, resulted in 64,502 ESKAPE pathogens. *S. aureus* was found to be the most abundant pathogen summing up to 38% of all the samples followed by *K. pneumoniae,* which accounted for 22.2% of the total isolates, from respiratory samples. However, *S. aureus* was still the most isolated species from all other samples as well (Ramsay, 2018).

Figure 1. Trends in the number of ESKAPE pathogens isolated from clinical samples



MODE OF ACTION OF ANTIBIOTICS

The antibiotics developed till present time work on either of the following targets on bacterial cells and mode of action. A schematic of the same is depicted in figure 2.

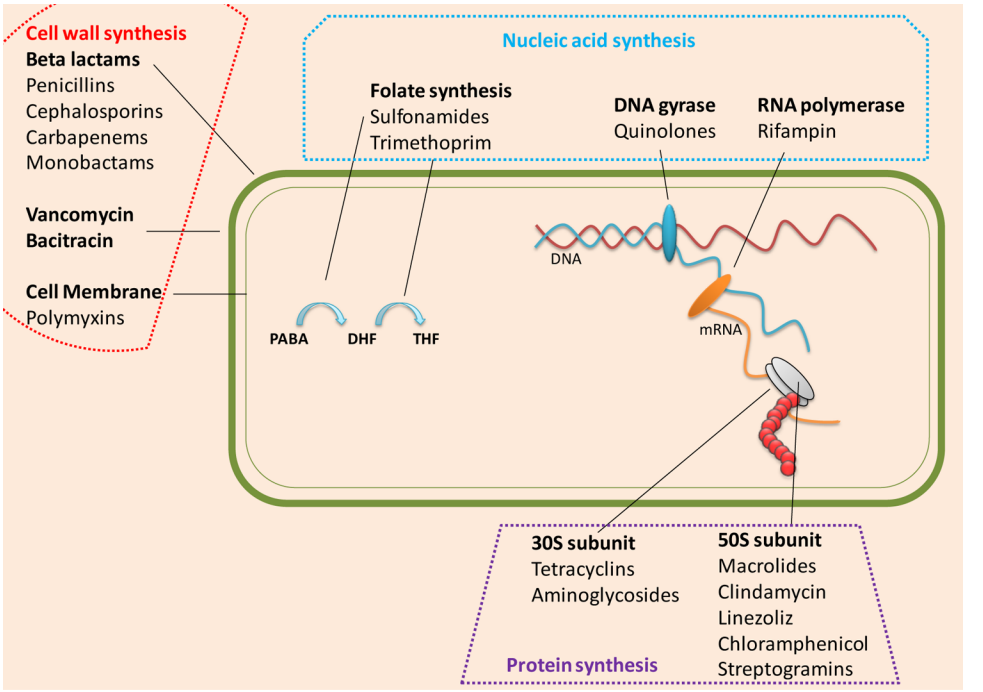
Inhibition of Cell Wall Synthesis

Many antibiotics, especially those with β-lactam rings in them, inhibit the cross-linking of the cell wall components. These antibiotics prevent the formation of the peptidoglycan layer of the bacterial cells, essential for their survival. This weakens the ability of bacterial cells to reproduce and affects their viability (Walsh, 2003). Antibiotics like, vancomycin, penicillin, etc. have a similar mode of action on bacterial pathogens.

Inhibition of Protein Synthesis and Translation

Many of the antibiotics target the process of protein synthesis in bacterial cells. The antibiotics act by binding to either 50S or 30S subunit of the ribosome, and in turn, stalling the process of protein biosynthesis. Many of the antibiotics like erythromycin, linezolid, tetracycline, etc. act on the bacterial mode through inhibiting protein synthesis pathway.

Figure 2. Schematic representation of the mode of antibiotic action
(DNA: deoxyribonucleic acid, mRNA: messenger ribonucleic acid, PABA:p-aminobenzoic acid, DHF: dihydrofolate, THF: tetrahydrofolate).



Inhibition of DNA Replication

DNA gyrase is an enzyme which unwinds the supercoiled DNA helices. Many of the antibiotics bind to these relaxed DNA structures and affect the process of replication. Quinolones are an example of such a class of antibiotics which binds to the nicked DNA, stabilizes it and in turn, prevents further repair of the system (Aldred, 2014).

Inhibition of Folate Biosynthesis

Folic acid is an indispensable nutrient for the synthesis of proteins and nucleic acids in bacterial cells. The synthesis of folic acid uses para-amino-benzoic acid (PABA) as substrate (Bourne, 2014). Many antibiotics of early times, used a structural analog of PABA, thus hindering the process of folate biosynthesis. Mostly the sulfa drugs, sulfonamides, used folate biosynthesis as a target for their mode of action.

MECHANISM OF RESISTANCE DEVELOPMENT IN MICROBES

There are several means by which a microbe attains resistant genes against antibiotics. These can be carried by bacterial plasmids, chromosomes, or transposons (Giedraitiene, 2011). An antimicrobial resistant gene can have any of the effects like, inactivating the antibiotic, alteration in the drug binding site, change in cell permeability affecting internalization of drugs and biofilm formation (Wright, 2005; Li & Nikaido, 2004; Wilson, 2014).

Bacteria produce enzymes which hydrolyze the β-lactam ring present in β-lactamases. Most of the clinically important β-lactamases are produced by Gram-negative bacteria which modifies and thus inactivates the antibiotics. Some β-lactamases include enzyme like CTX-M. These are clinically significant enzymes and are found among *K. pnemoniae, A. baumannii, P. aeruginosa* and *Enterobacter* spp. Among the list of ESKAPE pathogens. Some of the β-lactam enzymes show a high level of mutation among them and hence easily develop as a resistant gene. Another class of β-lactamases includes Metallo-β-lactamases, MBLs, which require zinc ions as a cofactor for their activity (Rice, 2010; Kumarasamy, 2010). These genes are generally present on the bacterial plasmids and hence are easily transferred from one to another organism.

Some bacteria modify their target site and thus avoid recognition by antibiotics. Mutations in genes coding for the antibiotic recognition causes a change in its active site, thereby losing the binding affinity. The penicillin-binding protein 2a (PBP2a) is uniquely identified in the resistant strains of *S.aureus* (Pucci, 2002). PBP is a cytoplasmic protein, highly expressed in the antibiotic sensitive *S.aureus* strains, while PBP2a is uniquely expressed in the resistant strains. The Gram-positive bacteria of the *Enterococcus* genus recognizes an acyl-D-Ala-D-Ala sequence for inhibition from glycopeptides (Giedraitiene, 2011; Tang, 2014). However, these organisms have been reported to adopt a mutation for antibiotic recognition and thus develop resistance to the presence of the antibiotic, enhancing growth in its presence.

The intake of antibiotic by bacterial pathogens leads to their clearance from the host. However, to develop resistance, bacterial pathogens reduce the intake and accumulation of antibiotics within its cells, which in turn result in resistant strains. The presence of diminished protein channels, reducing the entry of antibiotics inside cells and presence of efflux pumps, which prevents the accumulation of antibiotics inside the cell, are the two strategies used by bacterial cells to develop resistance against antibiotics.

Porin protein channels are found in the outer membrane of many gram-negative bacteria which allow the passage of many hydrophilic substances, including antibiotics inside the cell. The loss of this protein channel results in the development of resistance in bacteria. The loss of many such proteins has been reported in many

antibiotic susceptible bacteria. For example, OprD loss in *P. aeruginosa* makes it susceptible to imipenem (Fukuoka, 1993). The loss of OmpK35 and OmpK36 in multidrug-resistant strains of *K. pneumoniae* results in the development of resistance against many β-lactams (Thomson, 2005).

Efflux pumps constitute a group of proteins found in bacteria which act as exporters and help bacteria to expel out the antibiotics and prevent its accumulation in the cell or inter-membrane spaces. This action results in the clearance of the antibiotic from the cell diminishing its bactericidal effects. Most of the efflux pumps are multidrug transporters making the bacteria multidrug resistant. Till date, five different families of efflux pumps have been described, which include, ATP binding cassette (ABC) family, the small multidrug resistance family, the major facilitator superfamily, the resistance-nodulation-division (RND) family, and the multidrug and toxic compound extrusion family (Sun, 2014). The most common efflux pumps in gram-negative bacteria are of RND family. This efflux pump plays a key role in the development of multi-drug resistant strains as these help bacteria to expel out most of the antibiotics and compounds that are structurally unrelated (Nikaido, 2012). This pump is associated with resistance to a broad range of antibiotics, including fluoroquinolones, β-lactams, tetracycline, macrolides, chloramphenicol, and aminoglycosides. So, this type of efflux pump accounts to the emerging drug-resistant strains of ESKAPE pathogens, especially *K. pneumoniae, P. aeruginosa,* and *Enterobacter* spp.

Biofilms are protective layers formed by the growth of bacterial cells and their adhesion. The bacterial cells colonize on any surface or area and adhere together with the secretion of extracellular polymeric substances such as polysaccharides, proteins, lipids, and extracellular DNA (Sharma, 2014). These adhering cells form a protective layer, preventing the underlying microbes from the harsh external environment and the effect of antibiotics. It also modifies the internal environment of the cell, to inactivate the antibiotics, i.e., providing an environment with low O_2, low pH, high CO_2, and low water availability. These conditions favor the growth of the microbe on the one hand and demolish the effect of antibiotics on the other. The most common pathogens found in biofilms in a healthcare setting are *S. aureus, K. pneumonieae, A. baumannii, and P. aeruginosa* (Hoiby, 2010).

HERBAL MEDICATION: A NECESSITY

Herbal medications are the traditional means of treatment of any infection or disease, using sustainable energy sources, mostly plants, and plant products. The diverse range of plant species on planet Earth and its various secretions has helped mankind from earlier times in curing themselves from severe diseased conditions. In ancient times,

when the medicinal science practiced today was not so well developed, people used these plant parts or its extracts for treatment of various diseases including typhoid, cough, cold, etc. The Ayurvedic sciences deal with such natural medication systems for curing various illnesses. However, it has not been able to become the mainline source of treatment due to various reasons. Still, there are 1211 small molecule drugs developed from the year 1981-2014, that are from natural sources or derived from the same and interestingly, 59% of all drugs developed, to treat bacterial infections, were derived from natural products (Newman, 2016).

MEDICINAL PLANTS AND THEIR USES

There are many plants all over the world with many antibacterial and antiinflammatory properties. Some of them are listed below:

Adiantum Capillus-Veneris Linn. (Pteridaceae)

It is a fern commonly found in moist temperate regions of the Himalayas. It is used to treat urinary tract infections (UTIs) (Ishaq, 2014).

Artemisia Absinthium Linn. (Asteraceae)

The paste of its aerial plant parts is used topically to treat pruritus and inflammatory and infectious skin disorders. These plants are traditionally used since long for treatment of various diseases and have also been harnessed for the development of antimalarial and typhoid drugs (Khan, 2008; Hayat, 2009).

Berberis Lycium Royle (Berberidaceae)

It is a shrub, generally used to treat diseases related to digestive tracts such as diarrhea, cholera, and piles. Its bark is traditionally used for the treatment of oral infections, toothaches, and earaches (Malik, 2017, Abbasi, 2010).

Gentiana Olivieri Griseb. (Gentianaceae)

It is an herb found in the alpine and sub-alpine areas of the Himalayas. The roots of these plants are traditionally used for the treatment of urinary retention (Ali, 2009; Bano, 2014).

Martynia Annua Linn. (Martniaceae)

It is an herbaceous, glandular and erect herb, commonly known as "Picchu." Sufficient organic matters in soil favor the growth of these plants. The leaves of the plant are the most useful parts from the medicinal point of view as its paste is used for topical application on wounds and skin allergies and infections and its juice is used for gargling in sore throats (Santram, 2011; Dhingra, 2013).

Nerium Oleander Linn. (Apocynaceae)

It is found mostly in the Himalayan valleys. The young branches of the plant are used for curing oral infections (Hussain, 2004).

Pyrus Pashia Linn. (Rosaceae)

It is a woody plant of the rose family bearing fruits. It is used as a laxative and for the treatment of gastrointestinal, cardiovascular, and respiratory ailments (Janbaz, 2015)

Swertia Chirata Linn. (Gentianaceae)

It is a whole plant infusion used for the treatment of various infections of the digestive tract, skin, and respiratory tract (Kumar, 2016).

Zanthoxylum Armatum D.C. (Rutaceae)

It is commonly known as "timber." The young branches are chewed for the treatment of oral and dental infections, and the fruits and bark of the plant are used for the treatment of cancer and digestive ailments (Alam, 2017).

Ocimum Sanctum Linn. (Merr.) (Lamiaceae)

The plant is used since long for the treatment of various infections and diseases. It is the traditional plant for treatment of a wide range of inflammations. The phyto-constituents of the plant include alkaloids, flavonoids, tannins, and carbohydrates. The plant and intake of its several parts in different forms have proved to be effective against a wide variety of gram-positive as well as gram-negative pathogens. The methanol extracts and seed and leaf oils of this plant possess immune-modulatory properties; the leaves induce cytokine secretion and the linoleic acid of the plant bear analgesic, anti-pyretic, and anti-inflammatory properties (Bhatia, 2013; Kumar, 2011).

Cinnamomum Cassia (Linn.) J. Presl (Lauraceae)

The oil of this plant shown antimicrobial activities. It has been found effective against a wide variety of microbes like E. coli, H. pylori, etc. A mixture of extracts of Allium tuberosum Rottler ex Spreng; (Amaryllidaceae), C. cassia and Cornus officinalis Torr. ex Dur. (Cornaceae) has been studied to be effective against many foodborne microorganisms. The extract of its bark inhibits bacterial endotoxin activity and growth of Candida spp. responsible for emerging illness (Choi, 2001; Roopashree, 2008).

Curcuma Longa Linn. (Zingiberaceae)

It is a perennial herb. The roots of the plant have antibacterial, anti-inflammatory as well as anti-neoplastic activity due to the presence of various terpenoids and curcuminoids. Curcumins have antioxidant, antiinflammatory, antifungal activities. It is also reported to reduce the secretion of inflammation-inducing histamine, increases and prolongs the action of cortisol and improves circulation, which in turn assists the removal of toxins out of the body. The ethyl extract of the plant has shown to have a very strong antibacterial activity against MRSA strains at concentrations as low as 0.125-2 mg/mL (Kim, 2005).

Piper Nigrum Linn. (Piperaceae)

Commonly known as "black pepper," is found to be effective against many drug-resistant strains and can prove to be a successful hit if merged with organic or synthetic chemistry for making of new antimicrobials. Its ethanol and aqueous extracts are effective against penicillin-G resistant strains of *S. aureus*. Its fruit extracts have anti-mycobacterial activity against MDR *Mycobacterium tuberculosis (Mtb)* (Kim, 2005).

Syzygium Aromaticum (Linn.) Merrill & Perry (Myrtaceae)

Also known as "clove," is used as an antimicrobial agent against food spoilage bacteria and foodborne pathogens (S.aureus, P. aeruginosa, and E. coli). The essential oils of clove possess efficient antimicrobial activity against many gram-positive and gram-negative bacteria (Pandey & Singh 2011).

Aloe Vera Burm. F. (Asphodelaceae)

It is isolated from the mucilaginous part of the center of the leaf. The A. vera gel contains sugars, amino acids, vitamins A, B, C and E, enzymes, polysaccharides and minerals. B-sitosterol, acemannan, and glycoprotein of A. vera extract have therapeutic potentials. Research has proved its antibacterial efficacy against a wide range of gram-positive, gram-negative, and fungal populations (Alemdar, 2009).

Azadirachta Indica A. Juss. (Meliaceae)

It is traditionally known as neem, has beneficial effects on several skin ailments and bacterial infections. The methanol extracts of the plant have the highest efficacy as compared to other extracts in hexane, chloroform, etc. These extracts have proven to be more effective against gram-positive bacteria as compared to gram-negative bacteria. The antibacterial activity of A. indica plant extract has been shown for S. aureus, K. pneumonieae, P. aeruginosa among the ESKAPE pathogens (Sarmiento, 2011).

Tamarindus Indica Linn. (Fabaceae)

Tamarind has long been used since ancient times because of its antimicrobial and antiseptic properties. The constituents of the leaves of the tree-like flavonoids, xyloglucan, benzyl benzoate, Limonene, hexadecanol, and other polyphenol metabolites contribute to its antimicrobial activity (Escalona-Arranz, 2010).

Phyllanthus Emblica Linn. (Phyllanthaceae) and Coriandrum sativum Linn. (Apiaceae)

P. emblica and *C. sativum* are traditionally used in Indian homes as spices in foods. The fruit pulp of these plants has been researched to have antibacterial activity against 345 different bacterial isolates of 6 different Genera, most of them belonging to gram-negative type (Yakout, 2013).

Allium Cepa Linn. (Liliaceae) and Allium Sativum Linn. (Liliaceae)

The ethanol extracts of the cloves of these plants have antibacterial activities against MDR pathogens responsible for nosocomial infections. These extracts are active against most of the pathogens of ESKAPE pathogen list, especially S. aureus and P. aeruginosa (Azu, 2007).

Psidium Guajava Linn. (Myrtaceae)

Commonly known as guava, contain reducing sugars, alkaloids, saponins, tannins, terpenoids, and polyphenols for their antibacterial activity. The crude methanol extracts of the leaves and bark of the plant have been shown to have antibacterial activity against MDR *Vibrio cholerae* (Pandey & Shweta, 2011).

CONCLUSION

The infections and infectious pathogens are unavoidable. They can neither be skipped from the environment nor can they be tolerated by the normal human health. This increase in number of the infectious pathogens and a development of resistance in them with the same pace, calls for the identification of new targets for developing new antibiotics. The rise in population and exploitation of resources by the people, on the other hand, demands a sustainable source for these developments. Herbal medication, being a traditional and most ancient form of remedy used for various infections, needs much more promotion at the present scenario. It needs to bring herbal medication as the mainline treatment option for a prolonged health and medication with least side effects. If not alone, Ayurvedic sciences, in combination with synthetic and organic chemistry streams can bring itself to mainstream medication.

REFERENCES

Abbasi, A. M., Khan, M. A., Ahmed, M., & Zafar, M. (2010). Herbal medicines used to cure various ailments by the inhabitants of Abbottabad district, North West Frontier Province, Pakistan. *Indian Journal of Traditional Knowledge*, *9*, 175–183.

Alam, F., & Us Saqib, Q. N. (2017). Evaluation of *Zanthoxylum armatum* Roxb for *in vitro* biological activities. *Journal of Traditional and Complementary Medicine*, *7*(4), 515–518. doi:10.1016/j.jtcme.2017.01.006 PMID:29034201

Aldred, K. J., Kerns, R. J., & Osheroff, N. (2014). Mechanism of quinolone action and resistance. *Biochemistry*, *53*(10), 1565–1574. doi:10.1021/bi5000564 PMID:24576155

Alemdar, S., & Agaoglu, S. (2009). Investigation of *in vitro* antimicrobial activity of *aloe vera* juice. *Journal of Animal and Veterinary Advances*, *8*, 99–102.

Ali, H., & Qaiser, M. (2009). The ethnobotany of Chitral valley, Pakistan with particular reference to medicinal plants. *Pakistan Journal of Botany*, *41*, 2009–2041.

Azu, N. C., Onyeagba, R. A., Nworie, O., & Kalu, J. (2007). Antibacterial activity of *Allium cepa* (Onions) and *Zingiber officinale* (Ginger) on *Staphylococcus aureus* and *Pseudomonas aeruginosa* isolated from high vaginal swab. *Internet J Trop Med*, *3*(2), 2.

Balzarini, J., Schols, D., Neyts, J., van Damme, E., Peumans, W., & de Clercq, E. (1991). α-(1–3)-and α- (1–6)-D-mannose-specific plant lectins are markedly inhibitory to human immunodeficiency virus and cytomegalovirus infections *in vitro*. *Antimicrobial Agents and Chemotherapy*, *35*(3), 410–416. doi:10.1128/AAC.35.3.410 PMID:1645507

Bano, A., Ahmad, M., Hadda, T., Saboor, A., Sultana, S., Zafar, M., ... Ashraf, M. (2014). Quantitative ethnomedicinal study of plants used in the skardu valley at high altitude of Karakoram-Himalayan range, *Pakistan. Journal of Ethnobiology and Ethnomedicine*, *10*(1), 43. doi:10.1186/1746-4269-10-43 PMID:24885937

Bhatia, A. K., Kumar, A., Goel, A., Gupta, A., & Rahal, A. (2013). Antibacterial activity of hot aqueous extract of *Ocimum sanctum* leaves against common bacterial pathogens of animals. *Pharma Science Monitor*, *4*, 279–285.

Bourne, C. R. (2014). Utility of the biosynthetic folate pathway for targets in antimicrobial discovery. *Antibiotics (Basel, Switzerland)*, *3*(1), 1–28. doi:10.3390/antibiotics3010001 PMID:27025730

Choi, J., Lee, K. T., Ka, H., Jung, W. T., Jung, H. J., & Park, H. J. (2001). Constituents of the essential oil of the *Cinnamomum cassia* stem bark and the biological properties. *Archives of Pharmacal Research*, *24*(5), 418–423. doi:10.1007/BF02975187 PMID:11693543

Dhingra, A. K., Chopra, B., & Mittal, S. K. (2013). *Martynia annua* L.: A review on its ethnobotany, phytochemical and pharmacological profile. *Journal of Pharmacognosy and Phytochemistry*, *1*, 135–140.

Escalona-Arranz, J. C., Peres-Roses, R., Urdaneta-Laffita, I., Camacho-Pozo, M. I., Rodriguez-Amado, J., & Licea-Jimenez, I. (2010). Antimicrobial activity of extracts from *Tamarindus indica* L. leaves. *Pharm. Mag*, *6*(23), 242–247. doi:10.4103/0973-1296.66944 PMID:20931087

Fukuoka, T., Ohya, S., Narita, T., Katsuta, M., Iijima, M., Masuda, N., ... Nikaido, H. (1993). Activity of the carbapenem panipenem and role of the OprD (D2) protein in its diffusion through the *Pseudomonas aeruginosa* outer membrane. *Antimicrobial Agents and Chemotherapy*, *37*(2), 322–327. doi:10.1128/AAC.37.2.322 PMID:8452364

Giedraitiene, A., & Vitkauskien, ˙. E. (2011). Antibiotic resistance mechanisms of clinically important bacteria. *Medicina*, *47*(3), 137–146. doi:10.3390/medicina47030019 PMID:21822035

Hayat, M. Q., Khan, M. A., Ashraf, M., & Jabeen, S. (2009). Ethnobotany of the genus *Artemisia*, L. (Asteraceae) in Pakistan. *Ethnobotany Research and Applications*, *7*, 147–162. doi:10.17348/era.7.0.147-162

Høiby, N., Bjarnsholt, T., Givskov, M., Molin, S., & Ciofu, O. (2010). Antibiotic resistance of bacterial biofilms. *International Journal of Antimicrobial Agents*, *35*(4), 322–332. doi:10.1016/j.ijantimicag.2009.12.011 PMID:20149602

Hussain, M., & Gorsi, M. (2004). Antimicrobial activity of *Nerium oleander* Linn. *Asian J. Plant Sci.*, *3*(2), 177–180. doi:10.3923/ajps.2004.177.180

Ishaq, M. S., Hussain, M. M., Siddique Afridi, M., Ali, G., Khattak, M., & Ahmad, S. (2014). *In vitro* phytochemical, antibacterial, and antifungal activities of leaf, stem, and root extracts of *Adiantum capillus veneris. TheScientificWorldJournal*, *269793*. doi:10.1155/2014/269793 PMID:24592156

Janbaz, K. H., Zaeem Ahsan, M., Saqib, F., Imran, I., Zia-Ul-Haq, M., Abid Rashid, M., ... Moga, M. (2015). Scientific basis for use of *Pyrus pashia* Buch.-Ham. ex D. Don. fruit in gastrointestinal, respiratory and cardiovascular ailments. *PLoS One*, *10*(3), e0118605. doi:10.1371/journal.pone.0118605 PMID:25786248

Khan, S. W., & Khatoon, S. (2008). Ethnobotanical studies on some useful herbs of Haramosh and Bugrote valleys in Gilgit, northern areas of Pakistan. *Pakistan Journal of Botany*, *40*, 43–58.

Kim, K. J., Yu, H. H., Cha, J. D., Seo, S. J., Choi, N. Y., & You, Y. O. (2005). Antibacterial activity of *Curcuma longa* L. against methicillin-resistant *Staphylococcus aureus. Phytotherapy Research*, *19*(7), 599–604. doi:10.1002/ptr.1660 PMID:16161063

Kumar, A., Rahal, A., & Verma, A. K. (2011). *In-vitro* antibacterial activity of hot aqueous extract (HAE) of *Ocimum sanctum* (Tulsi) leaves. *Indian Journal of Veterinary Medicine*, *31*, 96–97.

Kumar, V., & Van Staden, J. (2016). A review of *Swertia chirayita* (Gentianaceae) as a traditional medicinal plant. *Frontiers in Pharmacology*, *6*, 308. doi:10.3389/fphar.2015.00308 PMID:26793105

Kumarasamy, K. K., Toleman, M. A., Walsh, T. R., Bagaria, J., Butt, F., Balakrishnan, R., ... Woodford, N. (2010). Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. *The Lancet. Infectious Diseases*, *10*(9), 597–602. doi:10.1016/S1473-3099(10)70143-2 PMID:20705517

Li, X. Z., & Nikaido, H. (2004). Efflux-mediated drug resistance in bacteria. *Drugs*, *64*(2), 159–204. doi:10.2165/00003495-200464020-00004 PMID:14717618

Llaca-Díaz, J. M., Mendoza-Olazarán, S., Camacho-Ortiz, A., Flores, S., & Garza-González, E. (2012). One-year surveillance of ESKAPE pathogens in an intensive care unit of monterrey, Mexico. *Chemotherapy*, *58*(6), 475–481. doi:10.1159/000346352 PMID:23548324

Malik, T. A., Kamili, A. N., Chishti, M. Z., Ahad, S., Tantry, M. A., Hussain, P. R., & Johri, R. K. (2017). Breaking the resistance of *Escherichia coli*: Antimicrobial activity of *Berberis lycium* Royle. *Microbial Pathogenesis*, *102*, 12–20. doi:10.1016/j.micpath.2016.11.011 PMID:27888048

Newman, D. J., & Cragg, G. M. (2016). Natural products as sources of new drugs from 1981 to 2014. *Journal of Natural Products*, *79*(3), 629–661. doi:10.1021/acs.jnatprod.5b01055 PMID:26852623

Nikaido, H., & Pages, J. M. (2012). Broad-specificity efflux pumps and their role in multidrug resistance of Gram-negative bacteria. *FEMS Microbiology Reviews*, *36*(2), 340–363. doi:10.1111/j.1574-6976.2011.00290.x PMID:21707670

Pandey, A., & Shweta. (2011). Antibacterial properties of *Psidium guajava* leaves, fruits and stems against various pathogens. *Int. J. Pharm. Res. Dev*, *3*, 15–24.

Pandey, A., & Singh, P. (2011). Antibacterial activity of *Syzygium aromaticum* (clove) with metal ion effect against food borne pathogens. *Asian J. Plant Sci. Res*, *1*, 69–80.

Pucci, M. J., & Dougherty, T. J. (2002). Direct quantitation of the numbers of individual penicillin-binding proteins per cell in *Staphylococcus aureus*. *Journal of Bacteriology*, *184*(2), 588–591. doi:10.1128/JB.184.2.588-591.2002 PMID:11751840

Ramsamy, Y., Essack, S. Y., Sartorius, B., Patel, M., & Mlisana, K. P. (2018). Antibiotic resistance trends of ESKAPE pathogens in Kwazulu-Natal, South Africa: A five-year retrospective analysis. *African Journal of Laboratory Medicine*, *7*(2), 887. doi:10.4102/ajlm.v7i2.887 PMID:30568908

Rice, L. B. (2010). Progress and challenges in implementing the research on ESKAPE pathogens. *Infection Control and Hospital Epidemiology*, *31*(1), S7–S10. doi:10.1086/655995 PMID:20929376

Roopashree, T. S., Dang, R., Rani, R. H. S., & Narendra, C. (2008). Antibacterial activity of antipsoriatic herbs: *Cassia tora, Momordica charantia* and *Calendula officinalis. International Journal of Applied Research in Natural Products*, *1*, 20–28.

Sakagami, H., Kushida, T., Makino, T., Hatano, T., Shirataki, Y., & Matsuta, T. (2012). Functional analysis of natural polyphenols and saponins as alternative medicines. Academic Press. doi:10.5772/30449

Santram, L., & Singhai, A. K. (2011). Preliminary pharmacological evaluation of *Martynia annua* Linn leaves for wound healing. *Asian Pacific Journal of Tropical Biomedicine*, *1*(6), 421–427. doi:10.1016/S2221-1691(11)60093-2 PMID:23569806

Sarmiento, W. C., Maramba, C. C., & Gonzales, M. L. M. (2011). An *in-vitro* study on the antibacterial effect of neem (*Azadirachta indica*) leaf extract on methicillin-sensitive and Methicillin-resistant *Staphylococcus aureus. PIDSP J.*, *12*, 40–45.

Sharma, G., Rao, S., Bansal, A., Dang, S., Gupta, S., & Gabrani, R. (2014). *Pseudomonas aeruginosa* biofilm: Potential therapeutic targets. *Biologicals*, *42*(1), 1–7. doi:10.1016/j.biologicals.2013.11.001 PMID:24309094

Sun, J., Deng, Z., & Yan, A. (2014). Bacterial multidrug efflux pumps: Mechanisms, physiology and pharmacological exploitations. *Biochemical and Biophysical Research Communications*, *2*(453), 254–267. doi:10.1016/j.bbrc.2014.05.090 PMID:24878531

Tang, S. S., Apisarnthanarak, A., & Hsu, L. Y. (2014). Mechanisms of *β*-lactam antimicrobial resistance and epidemiology of major community- and healthcare-associated multidrug resistant bacteria. A*dvanced Drug Delivery Reviews,* 7*8,* 3–13. doi:10.1016/j.addr.2014.08.003 PMID:25134490

Thomson, J. M., & Bonomo, R. A. (2005). The threat of antibiotic resistance in Gram-negative pathogenic bacteria: *β*-lactams in peril. C*urrent Opinion in Microbiology,* 8(5), 518–524. doi:10.1016/j.mib.2005.08.014 PMID:16126451

Walsh, C. (2003). *Antibiotics: Actions, Origins, Resistance*. Washington, DC: ASM Press. doi:10.1128/9781555817886

WHO. (2017). *Global priority list of antibiotic-resistant bacteria to guide research, discover, and development of new antibiotics*. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf

Wilson, D. N. (2014). Ribosome-targeting antibiotics and mechanisms of bacterial resistance. *Nature Reviews. Microbiology*, *1*(12), 35–48. doi:10.1038/nrmicro3155 PMID:24336183

Wright, G. D. (2005). Bacterial resistance to antibiotics: Enzymatic degradation and modification. *Advanced Drug Delivery Reviews*, *57*(10), 1451–1470. doi:10.1016/j.addr.2005.04.002 PMID:15950313

Yakout, S. M., Abd-Alrahman, S. H., Mostafa, A., & Salem-Bekhit, M. M. (2013). Antimicrobial effect of seed ethanolic extract of Coriander. *Journal of Pure & Applied Microbiology*, *7*, 459–463.

Chapter 11
Biogenic Synthesis of Gold Nanoparticles and Their Antimicrobial Activities

Snežana Radisavljević
https://orcid.org/0000-0003-0894-2118
Faculty of Science, University of Kragujevac, Serbia

Biljana Petrović
https://orcid.org/0000-0001-7914-6026
Faculty of Science, University of Kragujevac, Serbia

ABSTRACT

Gold nanoparticles (AuNPs) are widely used in biomedical applications, especially diagnostic and drug delivery. The antibacterial activity of nanoparticles depends on the dimensions of the particles. AuNPs may associate with the surface of the cell membrane and cause disorder such as respiration and permeability. The method of binding of particles for bacteria depends on their surface available for interaction. Smaller particles which have the larger surface area available for interaction will show better bactericidal effect than the larger particles. Useful antibacterial agents should also be toxic to various pathogenic bacteria with the ability to coat different surfaces like biomaterials, devices, textiles, food packaging, and so on. The biological and physiochemical properties of synthesized AuNPs have impact on the use of gold nanoparticles like antimicrobial agents, especially for water purification, as well as other biomedical applications.

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INTRODUCTION

Nanotechnology is the most investigated field in the last decades. A very spread usage (almost in every kind of technology and science) of nanotechnology makes this field the most interestig due to usage like cosmetics or drug delivery to electronics, sensing and catalysis (Grana *et al.,*2017). In the last decade, the big interest and demand among researches and chemist for metal nanoparticles is due to applications in photography, catalysis, optics as well as in other areas (Zhou *et al.,*2004). In the last few years, nanotechnology undergo enormous development in the field of methodologies for synthesis of nanoparticles with certain shape and size to meet the goal (Fang *et al.,*2010; Dhayalan *et al.,*2018). In markets it is possible to find more than 800 products connect with nanotechnology, and this number increase every day (Shedbalkar *et al.,*2014; Husen & Siddiqi, 2014).

Beside silver, the properties (electrical, photothermal and optical) of gold, make this element the most investigated. Until today, scienties found several ways to prepare AuNPs from different starting materials and various methods (Selvakannan *et al.,*2002; Sun & Xia, 2002). The previously described methods are limited due to disadvantages such as utilization of toxic substances, various pH values, temperatures, costly instruments or the process will give smaller yield. These disadvantages have impact on the researchers to make efforts to develop new profitable methods and eco-friendly acceptability (Hulkiere *et al.,*2017). Thus, currently it is necessary to synthesize new nanoparticles, where preparation does not include harmful substances. The most promising source of non-toxic chemicals can be plants or microorganisms, due to this fact plants or microorganisms will be used for biosynthesis in order to solve potential problem of destroying the environment (Kar *et al.,* 2014; Fatima *et al.,*2015). The green technology is the word used for synthesis of nanoparticles from natural sources (plants) without using toxic chemicals (Arunachalam & Annamalai, 2013). For the green synthesis the best choice is to use microbes such as bacteria or fungi in order to get novel nanomolecules (Shedbalkar *et al.,*2014; Sanna *et al.,*2014). The presence of elemental metal can be a good evidence for formation of nanoparticles. Therefore, the plant extract must contain certain type of chemicals which can reduce metal ion. The best choice is smelling plants or leaves, because they are made from chemicals which are capable for reduction (Husen & Siddiqi, 2014).

Plants have possibility to accumulate different metals (Jabeen *et al.,*2009). In some cases this promises to protect the plants from insects or herbivores. Nanoparticles can be used to prevent plant diseases and exibit growth of plants (Park *et al.,* 2007) as well as to diagnose various diseases. This can be helpful for plants which humans use every day (such as radish, rice, spinach and others) (Rico *et al.,* 2011). The high potential for the controlled release of drug, usage of trace elements without destroying

insects and similar, can be assigned to further development of nanotechnology (Nair *et al.,*2010).

The transport of drugs is closely connected with utilization of AuNPs (Bartneck *et al.,* 2010). For biological activity of nanoparticles, the size of particles has the crucial role. AuNPs may associate with the surface of the cell membrane and cause disorders such as respiration and permeability. Surface available for interaction is important to determine the method of binding of particles for bacteria. The size of particles is not so important, due to that some small particles can have larger free surface for interaction and show great medicinal effect, especialy bactericidal effect (Baker *et al.,* 2005). Useful antibacterial agent should also be toxic to various pathogenic bacteria but with ability to coat different surfaces, like biomaterials, devices, textiles, food packaging and so on. AuNPs can be used like antimicrobial agents due to various properties, with the greatest impact on water purification (Bindhu & Umadevi, 2014).

GREEN SYNTHESIS OF GOLD NANOPARTICLES (AuNPs) USING PLANTS

The procedure for synthesis of nanoparticles strongly depends on pH value, temperature, concentration of metal salt, but the most important is the concentration and type of plant or algae extracts. Different plant extracts can be starting material for green synthesis of AuNPs, because thay contain various reducing agent, phenols or flavonoides, which can provoke reduction. Some of them are *Toona ciliata* (Kaushik *et al.,*2012), *Chrysopogon zizanioides* (Arunachalam & Annamalai, 2013), *Solanum lycopersicum* (Bindhu & Umadevi, 2014), *Coleous forskohlii* (Dhazalan *et al.,*2018), *Benincasa hispida, Justicia gendarussa, Ocimum basilicum* (Pankaj & Subir, 2013), *Dioscorea bulbifera* (Sougata *et al.,*2011), *Cladosporium cladosporioides, Sargassum wightii* Greville ex J. Agarth (Hulkiere *et al.,*2017), *A. nilotica* (Rakhi *et al.,*2013), *P. rugulosum* (Amrita *et al.,* 2012), *T.chebula* (Kesarla *et al.,*2012), L. japonica (Nagajyothi *et al.,* 2014), *E. macrocarpa* (Gérrard *et al.,* 2013), *T. conoides* (Rajeshkumar *et al.,*2013), *H. rosa-sinensis* (Akbar *et al.,*2014), *H. anomala* (Sathish *et al.,* 2011), *C. pepo, M. crispa* (Krishnaraj *et al.,* 2014).

Curcubita Pepo Linn. (Curcubitaceae) and Malva Crispa Linn. (Malvaceae)

Ten grams *C. pepo* and *M. crispa* leaves were placed in the right amount of distilled H_2O and boiled in microwave oven for a short period of time. The synthesis of AuNPs is successful which can be concluded due to change of color from yellow to

pinkish violet. The obtained AuNPs was confirmed by UV-Vis absorbance and SPR band around 550 nm. Analogous absorbance band, was presented (Arunachalam & Annamalai, 2013). In order to get metal particles with the same dimensions, different concentration of leaves extracts were optimized. For nanoparticle synthesis 6 ml of extract in 44 ml of distilled water was used. Time for synthesis depends on extract, for curled mallow was necessary 120 min, while for pumpkin it was 150 min. During the incubation period, intensity of pinkish violet color increased. This observation can be due to the resonance (SPR) bands. In the case of control leaves extract alone, the change of color was not observed. Similarly, different concentrations of $HAuCl_4$ were used to get a maximum amount of AuNPs. Interestingly, presence of AuNPs was confirmed in the case of 1 mM $HAuCl_4$, peak was shifted in the case of 2 mM $HAuCl_4$ and presence of nanoparticles was not confirmed in the case of 3 mM $HAuCl_4$ (Mulvaney, 1996).

For nanoparticle synthesis pH value is also very important factor. At acidic pH (2), there was no absorption band without change and appearance of pinkish violet color, but at pH 3 the presence of color was confirmed, even in the spectrum absorption band was absent. At pH 4 to 6, both, color and bands were confirmed, but nanoparticles formation was absent. In alkaline pH (9-12), presence of color was very fast but without band from pH 9-11, band was shifted. For the higher amount of pH value color formation was very rapid (in the first ten minutes) after adding $HAuCl_4$ with the presence of band at 540 nm for pumpkin leaves. In the case of curled mallow, lower value of pH (around ten) confirmd presence of color and band, but less nanoparticles were formed. At neutral pH, and at pH 8, the reaction started imediatelly after adding $HAuCl_4$ and formation of nanoparticles was confirmed but no fast, 2 h 30 min for pumpkin and less time for curled mallow (2 h). Stability of newly synthesized AuNPs was investigated: 1 mM $HAuCl_4$ was added in the solution of leaves extract and distilled water, at pH 8, and UV-Vis spectra were recorded. The stability was examined in the presence of different acidic and alkaline solutions. The high stability of nanoparticles was confirmed by results of UV-Vis spectra (no change in the bands after 30 days of incubation). It is important to examine stability of particles before they are used for biological applications. Towards the optimization process, utilization of plant extracts can have great impact on dimension of nanoparticles and it was possible to get nanoparticles with the same dimensions (Krishnaraj *et al.,*2014). The various gram-positive (*Bacillus cereus, Staphylococus aureus, Listeria monocytogenes*) and gram-negative bacteria (*Escherichia coli, Salmonella typhi, S. enterica*) were used to investigate antimicrobial activity of new AuNPs. Interaction of AuNPs on these pathogens were studied using conductivity. Interactions of above mentioned bacteria with AuNPs (concentration 800 µg/ml) were shown high conductivity level (Oyewole & Abalaka, 2012).

Bio-TEM (Bio-Transmission Electron Microscope) was used to examine interaction of newly synthesized AuNPs and above mentioned bacteria. Bacterial cultures were exposed to AuNPs for 8 h and stained with negative staining. AuNPs had very bad impact on bacteria and destroy cell membranes.

Plant leaves extract must contain phytochemicals which are included in the synthesis of AuNPs. Depends on the concentration, chemical structure or availability, phytochemicals (alkaloids, saponins, steroids etc.) must have ability to reduce $HAuCl_4$. Presence of different phytochemicals was confirmed in aqueous extracts and these phytochemicals can be used to make nanoparticles with different benefits (biological application as well as antimicrobial) (Krishnaraj *et al.,*2014).

Turbinaria Conoides (Turner) J. Agarth (Sargassaceae)

The dried *T. conoides* (whole plants) were rinsed with water and then used for synthesis. The temperature of storage was -15°C and prepared extract can be used for several weeks. The extract was mixed with $AuCl_3$ in the ration 1:9 at ambiental temperature. The change of color was very rapid within 10 minutes, which can be the evidence for reduction or more precisely precence of AuNPs (Rajeshkumar *et al.,*2013). When gold ion disolves in water the color is yellow, but during reduction color gradually changed to dark pink. The change in color can be visible after one hour and the reduction usually completed after 24 h (the evidence for this is precipitation which appears after 24 h). The time for complete reduction depends on extract and can be very various, from 24 up to 120 h (Singaravelu *et al.,*2007; Mukherjee *et al.,*2002; Ahmad *et al.,*2003; Annamalai *et al.,* 2013). Successful synthesis can be confirmed by eyes (different colors of starting material and after reaction), but better evidence is UV-Vis spectra (range 350 – 700 nm). UV-Vis spectra presented band at 520 nm which can be assigned to SPR band of newly synthesized AuNPs. During the time intensity increases and the position of band shifts to 525 nm (blue shift 520 → 525 nm). This kind of shift can be connect with longitudinal excitation of SPR (Kamat *et al.,* 1998). Previously described theory depicts single SPR band like consequence of spherical shape and small dimension of nanoparticles which can be certified using TEM (Smitha *et al.,*2009). The conversion efficiency of gold into AuNPs after one hour is 90%, calculated according to absorbance intensity. Results of TEM analysis can be compared with results of the UV-Vis method. At the beginning of the synthesis spherical and undefined shapes of particles were observed, but after one day particles were changed and holded together to form bulky structure (Rajeshkumar *et al.,*2013).

Solanum Lycopersicum Linn. H. Karst. (Solanaceae)

S. lycopersicum is a commonly available fruit and can be used like fine source of different acids (malic, citric and ascorbic) (Ulrich, 1970). S. lycopersicum also contains different phytochemicals, some of them are very important carotinoides and polyphenols, which can have great impact on reduction of gold. The health benefits of *S. lycopersicum* can be observed because nutritients and phytochemicals have antioxidant properties and can make different combinations with lycopene. Utilization of S. lycopersicum can be connected with its anticancer characteristic (Polívkova *et al.,*2010), ability to reduce cardiovascular problems which can cause type 2 of diabetes (Shidfar *et al.,*2011) or possibility to be protective agent versus neurodegenerative diseases (Rao & Balachandran, 2002). The certain amount (0.1 kg) of S. lycopersicum after washing was smashed to get a specified dimension for extraction. The centrifugation was used for 10 min in order to eliminate insoluble particles. For further experiments the light yellow extract was collected. Various amount of starting material (fruit extracts, 5-15 ml) was mixed with aqueous solution of $HAuCl_4$ (3mM) and stirred at room temperature for 5 min. During this short period of time, color changed from colorless to brownish purple like evidence of synthesized AuNPs. UV-Vis absorption is one of the most employed method to determine presence of AuNPs due to appearance of band which is closely connected with surface plasmon excitation. This kind of SPR in the AuNPs indicates change of color during the synthesis. In heavy metals SPR was not observed, which indicated that SPR is the effect of small particles. Increasing of absorbance and blue shift of peak (from bigger to smaller value of wavelength) was consequence of adding increasing amount of fruit extract and indicate presence of nanoparticles (Bindhu & Umadevi, 2014).

Newly synthesized AuNPs were used to investigate their antimicrobial activity, against gram-negative (Pseudomonas aeruginosa) and gram-positive pathogen (S. aureus). Synthesized AuNPs were active against growth of both pathogens, afterwards pertinent antibacterial activity was revealed in all the bacteria. The highest activity was found for S. aureus. The difference in inbition may be depicted to various sensitivity of pathogens to the new AuNPs. Dimension of the particles has the crucial role in the antibacterial activity of nanoparticles. AuNPs can coat the surface of cell membranes which indicates changes in permeability or respiration. Surface available for interaction is important to determine method of binding of particles for bacteria. Better bactericidal effect is noticed at particles with free surface for interaction (Baker *et al.,*2005). Synthesized AuNPs possess various biological and physiochemical properties, with the greatest usage fo water purification (Bindhu & Umadevi, 2014).

Toona Ciliata M. Roem. (Melliaceae)

The extract of *T. ciliata* was rinsed with water and left at ambiental temperature until complete dryness (25 days). After that, it was crushed into fine powder, storage into plastic container and ready to be used for synthesis (Kaushik *et al.,*2012). Before synthesis of AuNPs, it is necessary to use standard methods of preliminary phytochemical tests (Khandelwal, 2008; Kokate *et al.,*2009). These tests are important to determine various metabolities, such as glycosides, tannins, steroids, flavonoids, alkaloids and carbohydrates, which must be present in extract (Gautam *et al.,*2010). All metabolites along with volatile oils and amino acids were present in extract. Extract solution (1 ml of 1% H_2O/MeOH) was placed into 20 ml of 1 mM $HAuCl_4$ in order to make AuNPs. Change of color was noticed immediately, suggesting the presence of newly synthesized AuNPs. This formation was confirmed by UV-Vis spectroscopy (band at 550 nm). The shape of peak (broad) is confirmation of polydispersity of AuNPs (using TEM analysis was possible to see well separated particles) (Kaushik *et al.,*2012).

Coleous Forskohlii Andrews (Lamiaceae)

The roots of C. forskohlii were washed and cut properly before they were left in the sunlight for some days. After drying, root pieces were smashed into fine powder, mixed with distilled water and heated at 100^{o}C for 2 min. The obtained powder was left at -20^{o}C, to be used for other investigations and synthesis. About 8g of powder prepared in this way, was placed in the right amount of water (0.1 l) and heated up to 100^{o}C for half hour, cooled down and filtered. A certain volume of obtained extract (1 ml) was placed in ten various tubes with 1×10^{-4} M $HAuCl_4$ in 0.1 to 1 ml range, and deionized water was used to get the final volume of 5 ml. pH value in the range of 7 to 13 was used to investigate the stability of newly synthesized AuNPs. The neutral pH value and 0.4 ml of obtained extract were the best conditions for synthesis. The modification of color which can be observed by eyes indicated the successful biogenic synthesis of AuNPs.

The well diffusion method was used to investigate antibacterial activity of AuNPs against different bacterial cultures (*P. vulgaris* and *M. luteus*). The various amounts of sample (250 – 1000 µg / mL) were put in wells made in the nutrient agar plate. Antibiotic tetracycline was used as standard solution. The plates were incubated at 37^{0}C for two days and inhibition zone diameter was measured. The zone diameter varies from 9-15 mm in P. vulgaris and 1-11mm in M. luteus at different concentrations while it was higher in case of tetracycline. This shows the antibacterial activity against both the bacterial strains (Dhayalan *et al.,*2018)

Hibiscus Rosa-Sinensis Linn. (Malvaceae)

The leaves were cut into pieces and placed into 0.1 l of water. The freshly prepared solution was mixed and placed into microwave for 3 min. The suspension was filtered and used for synthesis with 1 mM $AuCl_3$. The presence of reduction was noticed by eye (appearance of ruby red color) or by UV-Vis spectra (SPR band at 520 nm). With microwave technique the formation of AuNPs was very rapid and reduction was completed within a min (Akbar *et al.,*2014). This kind of heating is uniform and inhibit aggregation of the particles (Saifuddin *et al.,*2009). The huge impact on dimension of nanoparticles has the concentration of extract as well as microwave power. Intensity of absorbance became higher with the higher concentration of plant extract (up to 8%), but at higher concentration (up to 10%) intensity decreases. Logical explanation is that under the higher concentration, functional groups in extract are more available, so there is competition between metal ions and plant extract for reduction (Akbar *et al.,*2014).

Ideal conditions for synthesis are the 8% concentration of plant extract and 420 W of microwave power. At this condition, band at 520 nm shows up and slightly increase in intensity. Also, the shift in peak wavelength was not observed. This was the evidence of monodispersed particles, without any kind of aggregation (Rajeshkumar *et al.,*2013). Various solutions (0.2 M cysteine, 10% NaCl, phosphate buffer at pH 6, 7.4 and 8) were used to investigate stability of H. rosa-sinensis AuNPs. In every of this solutions peak shifts from 1 up to 8 nm. In-vitro stability was investigated at physiological pH and the obtained results shown good stability of AuNPs in biological fluids. To became in-vivo models AuNPs must go on different tests and have promising results. The first one and the most important is sterilization, in order to complete desolation of all organisms, such as virus, spores and bacteria (Akbar *et al.,*2014).

Sterilization is a critical step for *in-vivo* investigation and it explains the physicochemical properties. Consequently, autoclave at 120 ^{o}C for 15 min was used to sterilize AuNPs. The SPR band at approximately 520 nm was observed before and after sterilization process. The gold particles was quite stable, this was noticed according to the size of particles which was the same before and after sterilization. Flavonoids or water soluble compounds present in extract can be used to stabilize nanoparticles and have great impact on sterilization results (Philip *et al.,*2011).

Cladosporium Cladosporioides (Fresen.) G.A. de Vries

Gold metal salt was mixed with aqueous extract of *C. cladosporioides,* and it was kept for several hours for reduction of gold ions to AuNPs at ambient temperature. Successful biogenic synthesis can be monitored by eye, the color modification

was noticed (starting material is yellow and after reaction color is reddish violet) (Murphy *et al.,*2008). The main reason for color change was excitation of SPR of AuNPs (Sanna *et al.,*2014).

Four human pathogenic bacteria (*E. coli* MTCC 118, *B.subtilis* MTCC 441, *S. aureus* MTCC 7443, P. aeruginosa MTCC 424) and one fungal pathogen (*A. niger* MTCC 281) were used to determine antimicrobial activity (Shamaila *et al.,*2016). The petriplates seeded with microorganisms were used like starting material for adding AuNPs. Fluconazole and ampicillin (the both with the same concentration of 1 mg/ml) were used like standard probe. Incubation was at the temperature of human organism (37 ^{o}C) and after one day zone of inhibition was determined in mm.

The smaller inhibition was observed against *B. subtilis* (MTCC 441) The most active was against S. aureus (MTCC 7443). With the aim to explain interaction between AuNPs and pathogens, electron microscope was used to observe combination of interaction of AuNPs mixed with the microorganisms. Different mechanisms can be used to describe antimicrobial capability of AuNPs.

AuNPs can have great impact on cells (make a holes and the contents spill out) or can interact with DNA and inhibit the growth of the organism. The antimicrobial activity can be explained by production of free radicals or decreased activity of enzymes closely connect with interaction of thiol group with AuNPs (Fatima *et al.,*2015; Hussain *et al.,* 2005). Impact of AuNPs on various bacteria was studied before (Priyadarshini *et al.,* 2014; Syed *et al.,*2016; Gülçin, 2010). The new synthesized AuNPs using C. cladosporioides were also active against the both type of fungus and bacteria. This trait makes them a perfect candidate for developing different antimicrobial agent with great activity (Hulkiere *et al.,*2017).

Chrysopogon Zizanioides (Linn.) Roberty (Poaceae)

The leaves extract was washed with H_2O, soap and again with water, in order to remove impurity, and dryed at ambiental temperature until complete dryness (at least two weeks). After that it was smashed into powder and griddled to get uniform size. Leaf powder was placed into 0.1 l of distilled water and heated for short period of time (about 5 min). Further, it was filtered and storage into container (specific kind to protect extract from sunlight) and used for synthesis (Elavathagan & Arunachalam, 2011; Arunachalam *et al.,*2013). For synthesis leaf extract was placed into solution of 1 mM $HAuCl_4$ in ration 1:2. Formation of AuNPs was noticed due to change of color. Appearance of new color was noticed within two hours, which was the evidence of change of gold ion to metal gold. The consequence was SPR band in UV-Vis spectra at 540 nm. The intensity of color was increased during the time, due to faster kinetics. The whole process was performed at ambient temperature and finished after 8 h (Ravindran, *et al.,* 2013). Phytosterols and alkaloids (water soluble

components of *C. zizanoides*) are responsible for reduction of gold and formation of metal gold. This kind of leaf extract is easy available and not so expensive, so it can be promising and most represented extract for this purpose (Arunachalam & Annamalai, 2013).

Lonicera Japonica Thunb. (Caprifoliaceae)

The flower extract was prepared by mixing powdered flower and deionized water (1:10) and heated for 20 min. For the preparation of metal gold, flower extract was placed in 1mM $HAuCl_4$ (ration 1: 9.5) and heated 30 min at 60-70 ^oC (Nagajyothi *et al.,*2014).

Appearance of a different shade of color was the evidence of formation AuNPs. The absorption band at 550 nm was confirmed using UV-Vis as also reported by Joy *et al.,*(2012). At the beginning peak was not presented but after 6 min the peak at 550 nm appeared which shown beginning of AuNPs synthesis. After some period of time the intensity of absorption band increased. The new AuNPs were the same after some days of storage, indicating the stability of nanoparticles prepared in this way.

This type of synthesis is simple, low-cost, non-toxic, energy-efficient and environmentally bening process. *L. japonica* extract contains different organic compounds which can be included in the bioreduction and stabilization of gold nanoparticles. AuNPs have ability to interact with microorganisms and as a result they can act as antimicrobial agents. The antibacterial activity was examined against various bacteria and fungi. Zones of inhibition were for *B. subtilis* (7 mm), *C. albicans* (7 mm), *S. aureus* (8 mm), *S. cerevisiae* (8 mm) and *E. coli* (9 mm). It was very difficult to have inhibition zone of the both types of bacteria and fungi with AuNPs (Gu *et al.,* 2003).

CONCLUSION

The preparation of AuNPs using eco-friendly process is the giant step for nanotechnology. It is possible to sintesized AuNPs using different plant extracts and successful biogenic synthesis can be observed by eye (change of color) or by conventional UV-Vis method (band at 540 nm). The synthesis is simple, low-cost, non-toxic, energy-efficient and environmentally bening process, so the researches make efforts to investigate and use more this methods. The new syntesized AuNPs have ability to interact with microorganisms and as the result thay can act as antimicrobial agents, while some of them can be used in different biological experiments. Also, the coating of antibiotics with AuNPs can enhance their properties.

REFERENCES

Ahmad, A., Senapati, S., Khan, M. I., Kumar, R., Ramani, R., Srinivas, V., & Sastry, M. (2003). Intrecellular synthesis of gold nanoparticles by a novel alkalotolerant actinomycete Rhodococcus species. *Nanotechnology*, *14*(7), 824–825. doi:10.1088/0957-4484/14/7/323

Akbar, Y., Kumaraswamy, R., & Shanmugam, R. (2014). Optimization and stabilization of gold nanoparticles by using herbal plant extract with microwave heating. *Nano Convergence*, *1*(1), 12–18. doi:10.118640580-014-0012-8 PMID:28191395

Amrita, M., Suraj, K. T., & Soon-Il, Y. (2012). Fungus mediated synthesis of gold nanoparticles and their conjugation with genomic DNA isolated from *Escherichia coli* and *Staphylococcus aureus*. *Process Biochemistry*, *47*(5), 701–711. doi:10.1016/j.procbio.2012.01.017

Annamalai, A., Christina, V. L. P., Sudha, D., Kalpana, M., & Lakshmi, P. T. V. (2013). Green synthesis characterization and antimicrobial activity of AuNPs using Euphobia hitra L. leaf extract. *Colloids and Surfaces. B, Biointerfaces*, *108*, 60–65. doi:10.1016/j.colsurfb.2013.02.012 PMID:23528605

Arunachalam, K. D., & Annamalai, S. K. (2013). Chrysopogon zizanioides aqueous extract mediated synthesis characterization of crystalline silver and gold nanoparticles for biomedical applications. *International Journal of Nanomedicine*, *8*, 2375–2384. doi:10.2147/IJN.S44076 PMID:23861583

Arunachalam, K. D., Annamalai, S. K., & Hari, S. (2013). One-step green synthesis and characterization of leaf extracts-mediated biocompatible silver and gold nanoparticles from Memocylon umbellatus. *International Journal of Nanomedicine*, *8*, 307–315.

Baker, C., Pradhan, A., Pakstis, L., Pochan, D. J., & Ismat, S. S. (2005). Synthesis and antibacterial properties of silver nanoparticles. *Journal of Nanoscience and Nanotechnology*, *5*(2), 244–249. doi:10.1166/jnn.2005.034 PMID:15853142

Bartneck, M., Keul, H. A., Singh, S., Czaja, K., Bornemann, J., Bockstaller, M., ... Groll, J. (2010). Rapid uptake of gold nanorods by primary human blood phagocytes and immunomodulatory effects of surface chemistry. *ACS Nano*, *4*(6), 3073–3086. doi:10.1021/nn100262h PMID:20507158

Bindhu, M. R., & Umadevi, M. (2014). Silver and gold nanoparticles for sensor and antibacterial applications. *Spectrochimica Acta. Part A: Molecular and Biomolecular Spectroscopy*, *128*, 37–45. doi:10.1016/j.saa.2014.02.119 PMID:24657466

Brooks, R. R., Chambers, M. F., Nicks, L. J., & Robinson, B. H. (1998). Phytomining. *Trends in Plant Science*, *3*(9), 359–362. doi:10.1016/S1360-1385(98)01283-7

Burygin, G. L., Khlebtsov, B. N., Shantrokha, A. N., Dykman, L. A., Bogatyrev, V. A., & Khlebtsov, N. G. (2009). On the enhanced antibacterial activity of antibiotics mixed with gold nanoparticles. *Nanoscale Research Letters*, *4*(8), 794–801. doi:10.100711671-009-9316-8 PMID:20596384

Dhayalan, M., Denison, M. I. J., Ayyar, M., Gandhi, N. N., Krishnan, K., & Baykal, A. (2018). Biogenic synthesis, characterization of gold and silver nanoparticles from Coleus forskohlii and their clinical importance. *Journal of Photochemistry & Photobiology*, *183*, 251–257. doi:10.1016/j.jphotobiol.2018.04.042 PMID:29734113

Elavathagan, T., & Arunachalam, K. D. (2011). Memecylon edule leaf extract mediated green synthesis of silver and gold nanoparticles. *International Journal of Nanomedicine*, *6*, 1265–1278. doi:10.2147/IJN.S18347 PMID:21753878

Fang, F., Kennedy, J., Carder, D. A., Futter, J., Murmu, P., & Markwitz, A. (2010). Modulation of field emission properties of ZnO nanorods during arc discharge. *Journal of Nanoscience and Nanotechnology*, *10*(12), 8239–8243. doi:10.1166/jnn.2010.3009 PMID:21121322

Fatima, F., Bajpai, P., Pathak, N., Singh, S., Priya, S., & Verma, S. R. (2015). Antimicrobial and immunomodulatory efficacy of extracellularly synthesized silver and gold nanoparticles by a novel phosphate solubilizing fungus *Bipolaris tetramera. BMC Microbiology*, *15*(1), 52–61. doi:10.118612866-015-0391-y PMID:25881309

Galbraith, D. W. (2007). Nanobiotechnology: Silica breaks through in plants. *Nature Nanotechnology*, *2*(5), 272–273. doi:10.1038/nnano.2007.118 PMID:18654282

Gautam, A., Jhade, D., Ahirwar, D., Sujane, M., & Sharma, G. N. (2010). Pharmacognostic evaluation of Toona ciliata bark. *Journal of Advanced Pharmaceutical Technology & Research*, *1*, 216–220. PMID:22247848

Gérrard, E. J. P., Peter, C., Xuan, L., & Derek, F. (2013). Green biosynthesis of gold nanometre scale plates using the leaf extracts from an indigenous Australian plant *Eucalyptus macrocarpa. Gold Bulletin*, *46*(3), 165–173. doi:10.100713404-013-0096-7

Grana, S. G., Ameneira, M. P., Vecino, X., Santos, I. P., Juste, J. P., Cruz, J. M., & Moldes, A. B. (2017). Biogenic synthesis of metal nanoparticles using a biosurfactant extracted from corn and their antimicrobial properties. *Nanomaterials (Basel, Switzerland)*, *7*(6), 139–152. doi:10.3390/nano7060139 PMID:28587297

Gu, H., Ho, P. L., Edmond, T., Ling, W., & Xu, B. (2003). Presenting vancomycin on nanoparticles to enhance antimicrobial activities. *Nano Letters*, *3*(9), 1261–1263. doi:10.1021/nl034396z

Gülçin, I. (2010). Antioxidant properties of resveratrol: A structure–activity insight. *Innovative Food Science & Emerging Technologies*, *11*(1), 210–218. doi:10.1016/j.ifset.2009.07.002

Huang, W. C., Tsai, P. J., & Chen, Y. C. (2007). Functional gold nanoparticles as photothermal agents for selective-killing of pathogenic bacteria. *Nanomed.*, *2*(6), 777–787. doi:10.2217/17435889.2.6.777 PMID:18095845

Hulkiere, M. M., Joshi, C. G., Ananda, D., Poyya, J., Kudva, A. K., & Dhananjaya, B. L. (2017). Biogenic synthesis of gold nanoparticles by marine endophytic fungus-*Cladosporium cladosporioides* isolated from seaweed and evaluation of their antioxidant and antimicrobial properties. *Process Biochemistry*, *63*, 137–144. doi:10.1016/j.procbio.2017.09.008

Husen, A., & Siddiqi, K. S. (2014). Phytosynthesis of nanoparticles: Concept, controversy and application. *Nanoscale Research Letters*, *9*(1), 229–252. doi:10.1186/1556-276X-9-229 PMID:24910577

Hussain, S. M., Hess, K. L., Gearhart, J. M., Geiss, K. T., & Schlager, J. J. (2005). In vitro toxicity of nanoparticles in BRL 3A rat liver cells. *Toxicology In Vitro*, *19*(7), 975–983. doi:10.1016/j.tiv.2005.06.034 PMID:16125895

Ibrahim, H. M. M. (2015). Green synthesis and characterization of silver nanoparticles using banana peel extract and their antimicrobial activity against representative microorganisms. J. Radiat. *Res. Appl. Sci.*, *8*, 265–275.

Jabeen, R., Ahmad, A., & Iqbal, M. (2009). Phytoremediation of heavy metals: Physiological and molecular aspects. *Botanical Review*, *75*(4), 339–364. doi:10.100712229-009-9036-x

Joy, S., Sandipan, R., Dipankar, C., Aparna, L., & Krishnendu, A. (2012). Mycogenesis of gold nanoparticles using a phytopathogen *Alternaria alternata*. Bioproc. *Biosystems Engineering*, *35*, 637–643.

Kamat, P. V., Flumiani, M., & Hartland, G. V. (1998). Picosecond dynamics of silver nanoclusters. Photoejection of electrons and fragmentation. *The Journal of Physical Chemistry B*, *102*(17), 3123–3128. doi:10.1021/jp980009b

Kar, P. K., Murmu, S., Saha, S., Tandon, V., & Acharya, K. (2014). Anthelmintic efficacy of gold nanoparticles derived from a phytopathogenic fungus, *Nigrospora oryzae*. *PLoS One*, *9*(1), e84693. doi:10.1371/journal.pone.0084693 PMID:24465424

Kaushik, R., Mann Avninder, S., Sandhu, B. S., & Parihar, V. B. S. (2012). Green synthesis of gold nanoparticles using *Toona ciliata* methanol bark extract and their characterisation. *International research*. *Journal of Pharmaceutics*, *9*, 115–119.

Kesarla, M. K., Badal, K. M., Madhulika, S., & Varadhan, K. (2012). *Terminalia chebula* mediated green and rapid synthesis of gold nanoparticles. *Spectrochimica Acta. Part A: Molecular and Biomolecular Spectroscopy*, *86*, 490–494. doi:10.1016/j.saa.2011.11.001 PMID:22130557

Khandelwal, K. R. (2008). *Practical Pharmacognosy-Techniques and Experiments* (19th ed.). Pune: Nirali Prakashan.

Kokate, C. K., Purohit, A. P., & Gokhale, S. B. (2009). Text book of Pharmacognosy (44th ed.). New Delhi: Nirali Prakashan.

Krishnaraj, C., Seonhwa, S., & Soon-Il, Y. (2014). Effect of size and shape controlled biogenic synthesis of gold nanoparticles and their mode of interactions against food borne bacterial pathogens. *Arabian Journal of Chemistry*.

Kumar, R., Roopan, S. M., Prabhakarn, A., Khanna, V. G., & Chakroborty, S. (2012). Agricultural waste Annona squamosa peel extract: Biosynthesis of silver nanoparticles. *Spectra Acta. A Mol. Biomol. Spectrosc.*, *90*, 173–176. doi:10.1016/j.saa.2012.01.029 PMID:22336049

McGrath, S. P., & Zhao, F. J. (2003). Phytoextraction of metals and metalloids from contaminated soils. *Current Opinion in Biotechnology*, *14*(3), 277–282. doi:10.1016/S0958-1669(03)00060-0 PMID:12849780

Mukherjee, P., Senapati, S., Mandal, D., Ahmad, A., Khan, M. I., Kumar, R., & Sastry, M. (2002). Extracellular synthesis of gold nanoparticles by the fungus Fusarium oxysporum. *ChemBioChem*, *3*(5), 461–463. doi:10.1002/1439-7633(20020503)3:5<461::AID-CBIC461>3.0.CO;2-X PMID:12007181

Mulvaney, P. (1996). Surface plasmon spectroscopy of nanosized metal particles. *Langmuir*, *12*(3), 788–800. doi:10.1021/la9502711

Murphy, C. J., Gole, A. M., Stone, J. W., Sisco, P. N., Alkilany, A. M., Goldsmith, E. C., & Baxter, S. C. (2008). Gold nanoparticles in biology: Beyond toxicity to cellular imaging. *Accounts of Chemical Research*, *41*(12), 1721–1730. doi:10.1021/ar800035u PMID:18712884

Nagajyothi, P. C., Lee, K. D., & Speekanth, T. V. M. (2014). Biogenic synthesis of gold nanoparticles (uasi-spherical, triangle, and hexagonal) using *Lonicera japonica* flower extract and its antimicrobial activity. *Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry*, *44*(7), 1011–1018. doi:10.1080/15533174.2013.797456

Nagraj, B., Divya, T. K., Barasa, M., Krshnamurthy, N. B., Dinesh, R., Negrila, C. C., & Predoi, D. (2012). Phytosynthesis of gold nanoparticles using *Caesalpina pulcherrima* (peacock flower) flower extract and evaluation of their antimicrobial activities. *Digest Journal of Nanomaterials and Biostructures*, *7*, 899–905.

Nair, R., Varghese, S. H., Nair, B. G., Maekawa, T., Yoshida, Y., & Kumar, D. S. (2010). Nanoparticulate material delivery to plants. *Plant Science*, *179*(3), 154–163. doi:10.1016/j.plantsci.2010.04.012

Nirmala, G. A., & Pandian, K. (2007). Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles-A brief study. *Colloids and Surfaces. A, Physicochemical and Engineering Aspects*, *297*(1-3), 63–70. doi:10.1016/j.colsurfa.2006.10.024

Nisha, S. N., Aysha, O. S., Rahaman, J. S. N., Kumar, P. V., Valli, S., Nirmala, P., & Reena, A. (2014). Lemon peels mediated synthesis of silver nanoparticles and its antidermatophytic activity. Spectra Acta. *A Mol. Biomol. Spectrosc.*, *124*, 194–198. doi:10.1016/j.saa.2013.12.019

Oyewole, O. A., & Abalaka, M. E. (2012). Antimicrobial activities of *Telfairia occidentalis* (fluted pumpkins) leaf extract against selected intestinal pathogens. *Journal of Health Sciences (Sarajevo)*, *2*, 1–4.

Pankaj, K. S., & Subir, K. (2013). Biosynthesis of elixir of life (gold nanoparticles) from plants. *Journal of Environmental Nanotechnology*, *2*, 52–62.

Park, H. J., Kim, S. H., Kim, H. J., & Choi, S. H. (2007). A new composition of nanosized silica-silver for control of various plant diseases. *Plant Pathology*, *22*(3), 295–320. doi:10.5423/PPJ.2006.22.3.295

Philip, D., Unni, C., Aromal, S. A., & Vidhu, V. K. (2011). *Murraya Koenigii* leaf-assisted rapid green synthesis of silver and gold nanoparticles. *Spectrochimica Acta. Part A: Molecular Spectroscopy*, *78*(2), 899–904. doi:10.1016/j.saa.2010.12.060 PMID:21215687

Polívková, Z., Šmerák, P., Demová, H., & Houška, M. (2010). Antimutagenic effects of lycopene and tomato purée. *Journal of Medicinal Food*, *13*(6), 1443–1450. doi:10.1089/jmf.2009.0277 PMID:20874227

Priyadarshini, E., Pradhan, N., Sukla, L. B., & Panda, P. K. (2014). Controlled synthesis of gold nanoparticles using *Aspergillus terreus* IF0 and its antibacterial potential against gram negative pathogenic bacteria. *Journal of Nanotechnology*, *2014*, 1–9. doi:10.1155/2014/653198

Rai, A., Prabune, A., & Perry, C. C. (2010). Antibiotic mediated synthesis of gold nanoparticles with potent antimicrobial activity and their application in antimicrobial coatings. *Journal of Materials Chemistry*, *20*(32), 6789–6798. doi:10.1039/c0jm00817f

Rajeshkumar, S., Malarkodi, C., Gnanajobitha, G., Paulkumar, K., Vanaja, M., Kannan, C., & Annadurai, G. (2013). Seaweed-mediated synthesis of gold nanoparticles using *Turbinaria conoides* and its characterization. *Journal of Nanostructure in Chemistry*, *3*(1), 44. doi:10.1186/2193-8865-3-44

Rajeshkumar, S., Malarkodi, C., Vanaja, M., Gnanajobitha, G., Paulkumar, K., Kannan, C., & Annadurai, G. (2013). Antibacterial activity of algae mediated synthesis of gold nanoparticles from Turbinatia conoides. *Der Pharma Chemica*, *5*, 224–229.

Rakhi, M., Braja, G. B., & Nabasmita, M. (2013). *Acacia nilotica* (babool) leaf extract mediated size-controlled rapid synthesis of gold nanoparticles and study of its catalytic activity. *International Nano Letters*, *3*(1), 53–58. doi:10.1186/2228-5326-3-53

Rao, A. V., & Balachandran, B. (2002). Role of oxidative stress and antioxidants in neurodegenerative diseases. *Nutritional Neuroscience*, *5*(5), 291–309. doi:10.1080/1028415021000033767 PMID:12385592

Ravindran, A., Chandran, P., & Khan, S. S. (2013). Biofunctionalized silver nanoparticles: Advances and prospects. *Colloids and Surfaces. B, Biointerfaces*, *105*, 342–352. doi:10.1016/j.colsurfb.2012.07.036 PMID:23411404

Rico, C. M., Majumdar, S., Duarte, G. M., Peralta, V. J. R., & Gardea, T. J. L. (2011). Interaction of nanoparticles with edible plants and their possible implications in the food chain. *Journal of Agricultural and Food Chemistry*, *59*(8), 3485–3498. doi:10.1021/jf104517j PMID:21405020

Saifuddin, N., Wong, C. W., & Yasumira, A. A. N. (2009). Rapid biosynthesis of silver nanoparticles using culture supernatant of bacteria with microwave irradiation. *E-Journal of Chemistry*, *6*(1), 61–70. doi:10.1155/2009/734264

Sanna, V., Pala, N., Dessì, G., Manconi, P., Mariani, A., Dedola, S., & Sechi, M. (2014). Single-step green synthesis and characterization of gold-conjugated polyphenol nanoparticles with antioxidant and biological activities. *International Journal of Nanomedicine*, *9*, 4935–4951. PMID:25364251

Sathish, K. K., Amutha, R., Palaniappan, A., & Sheela, B. (2011). Synthesis of gold nanoparticles: An ecofriendly approach using *Hansenula anomala. ASC Applied Materials & Interfaces*, *3*(5), 1418–1425. doi:10.1021/am200443j PMID:21517037

Selvakannan, P. R., Mandal, S., Pasricha, R., Adyanthaya, S. D., & Sastry, M. (2002). One-step synthesis of hydrophobized gold nanoparticles of controllable size by the reduction of aqueous chloroaurate ions by hexadecylaniline at the liquid-liquid interface. *Chemical Communications*, *13*(13), 1334–1335. doi:10.1039/b203438g

Shamaila, S., Zafar, N., Riaz, S., Sharif, R., Nazir, J., & Naseem, S. (2016). Gold nanoparticles: An efficient antimicrobial agent against enteric bacterial human pathogen. *Nanomaterials (Basel, Switzerland)*, *6*(4), 71–80. doi:10.3390/nano6040071 PMID:28335198

Shedbalkar, U., Singh, R., Wadhwani, S., Gaidhani, S., & Chopade, B. A. (2014). Microbial synthesis of gold nanoparticles: Current status and future prospects. *Advances in Colloid and Interface Science*, *209*, 40–48. doi:10.1016/j.cis.2013.12.011 PMID:24456802

Shidfar, F., Froghifar, N., Vafa, M., Rajab, A., Hosseini, S., Shidfar, S., & Gohari, M. (2011). The effects of tomato consumption on serum glucose, apolipoprotein B, apolipoprotein A-I, homocysteine and blood pressure in type-2 diabetic patients. *International Journal of Food Sciences and Nutrition*, *62*(3), 289–294. doi:10.3109/09637486.2010.529072 PMID:21138408

Shrivastava, S., Bera, T., Roy, A., Singh, G., Ramachandrarao, P., & Dash, D. (2007). Characterization of enhanced antibacterial effects of novel silver nanoparticles. *Nanotechnology*, *18*(22), 103–112. doi:10.1088/0957-4484/18/22/225103

Singaravelu, G., Arockiyamari, J., Ganesh, K. V., & Govindaraju, K. (2007). A novel extracellular biosynthesis of monodisperse gold nanoparticles using marine algae, *Sargassum wightii* Greville. *Colloids and Surfaces. B, Biointerfaces*, *57*(1), 97–101. doi:10.1016/j.colsurfb.2007.01.010 PMID:17350236

Smitha, S. L., Philip, D., & Gopchandran, K. G. (2009). Green synthesis of gold nanoparticles using Cinnamomum zeylanicum leaf broth. *Spectrochimica Acta. Part A: Molecular and Biomolecular Spectroscopy*, *74*(3), 735–739. doi:10.1016/j.saa.2009.08.007 PMID:19744880

Sougata, G., Sumersing, P., Mehul, A., Rohini, K., Amit, J., Sangeeta, K., & Balu, A. C. (2011). Synthesis of silver nanoparticles using *Dioscorea bulbifera* tuber extract and evaluation of its synergistic potential in combination with antimicrobial agents. *Journal of Nanomaterials*, *7*, 483–496.

Sun, Y., & Xia, Y. (2002). Shape-controlled synthesis of gold and silver nanoparticles. *Science*, *298*(5601), 2176–2179. doi:10.1126cience.1077229 PMID:12481134

Syed, B., Prasad, N. M. N., & Satish, S. (2016). Endogenic mediated synthesis of gold nanoparticles *bearing bactericidal activity. Journal of Microscopy and Ultrastructure*, *4*(3), 162–166. doi:10.1016/j.jmau.2016.01.004 PMID:30023223

Ulrich, R. (1970). Organic Acids. *The Biochemistry of Fruits and Their Products*, 89-118.

Zhang, W. X. (2003). Nanoscale iron particles for environmental remediation: An overvies. *J Nano Res*, *5*(3/4), 323–332. doi:10.1023/A:1025520116015

Zheng, L., Hong, F., Lu, S., & Liu, C. (2005). Effect of nano-TiO_2 on strenght of naturally aged seeds and *growth of spinach. Biological Trace Element Research*, *104*(1), 83–91. doi:10.1385/BTER:104:1:083 PMID:15851835

Zhou, Z., Qi, H., Matsuda, N., Honma, I., Shimada, K., Takatsu, A., & Kato, K. (2004). Characterization of gold nanoparticles synthesized using sucrose by seeding formation in the solid phase and seeding growth in aqueous solution. *Journal of Physical Chemistry*, *108*(22), 7006–7011. doi:10.1021/jp035972i

Section 3
Bioactive Compounds and Natural Products

Chapter 12
Pharmacological Properties of Curcumin:
Solid Gold or Just Pyrite?

Anuradha Singh
https://orcid.org/0000-0002-8145-1369
Sadanlal Sanwaldas Khanna Girls' Degree College, India & University of Allahabad, Prayagraj, India

ABSTRACT

Curcumin, the polyphenol natural product, is a constituent of the traditional medicine known as turmeric. Extensive research over the last 50 years has indicated that this polyphenol displays potent pharmacological effects by targeting many critical cellular factors through a diverse array of mechanisms of action. However, there are some obstacles that prevent this wonder molecule to be effective in clinical settings and limit its use to topical applications only. Curcumin has recently been classified as both PAINS (panassay interference compounds) and an IMPS (invalid metabolic panaceas) candidate. Due to likely false activity of curcumin in vitro and in vivo has resulted unsuccessful clinical trial of curcumin against several disease. The chapter will review the essential medicinal chemistry of curcumin as well as envisage a compilation and discussion on the poor bioavailability of curcumin.

INTRODUCTION

The natural products are secondary metabolites belongings to structurally diverse categories which are produced by the plants by evolutionary and adaptive processes over millions of years. Natural products (secondary metabolites) have been the most

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vital source of potential drug and their pharmacological properties have been well documented from ancient times. The different ethnic societies and experience of many generations of physicians is the root for the use of natural products to prevent or to cure diseases (Dias *et al.,* 2012; Bernardini *et al.,* 2018). At present, only 20% of people can afford modern medicine, the main concern is that most of them are ineffective and has numerous side effects. Although over hundreds of natural products from plant sources are used in modern medicine but in most of the cases their scientific evidence is lacking. However, today it is an unmet need to provide scientific evidence as to whether or not it is justified to use a plant or its active principles. Further, the characterization of bioactive plant preparations is must to validate their pharmacological activity and toxicity followed by clinical studies.

Thus, it is essential to correlate the pharmacological mechanism under *in vitro* and *in vivo settings* of any natural drug with clinical studies which can be achieved through healthy human volunteers. These clinical studies should be in a controlled manner, to verify the fact that whether or not active components of the plant would prevent or treat diseases in man. Having this in mind the author reviewed the literature available on *C. longa* and tried to critically evaluate the scientific data (David *et al.,* 2015; Patridge *et al.,* 2016; Sarkar *et al.,* 2019).

BACKGROUND

Turmeric is well known as Haldi (in Hindi), a spice which is one of the main constituents curcumin, a polyphenolic secondary metabolite. It is obtained from the rhizome of perennial herb *C. longa* related to Zingiberaceae family. Ravindran *et al.,* (2007); reported that more than 100 Curcuma species are listed in botanical sources; and among them, *C. longa* is the best one. *C. aromatic*, *C. phaeocaulis*, *C. zedoaria* and *C. caesia* are the other sources of curcumin. Aggarwal *et al.,* (2007), reported several synonyms of curcumin on the basis of its appearance and uses (**Table 1**).

Curcumin is widely cultivated in tropical and subtropical areas such as Southeast Asia mostly in India and China. India is the main producer of the turmeric and produces nearly the whole world's crop and uses 80% of it (Bao *et al.,* 2010; Labban, 2014). In the traditional medicine system of India, various *Curcuma* species have been used for the treatment of different diseases and health-related disorders. It has been also received interest from both the medical/scientific world and from culinary enthusiasts. Some of the uses of *Curcuma* species listed in **Table 2 (***Ayati et al., 2019)*.

Table 1. Synonyms of curcumin on the basis of its appearance and uses

S.No.	Synonyms of curcumin	Meaning
1	*Haridra (in Sanskrit)*	dear to Hari or Lord Krishna
2	*Pita*	(yellow, leading to the name Peethamberdhari for Lord Krishna based on wearing only yellow clothes)
3	*Gauri*	Brilliant
4	*Kanchani*	looks like gold
5	*Nisha*	beautiful as a full moon night
6	*Krimighni*	antibacterial and antihelminthic
7	*Mahaghni*	antidiabetic
8	*Yoshitpriya*	gynaecological disorders

Physicochemical Attributes of Curcumin

Curcumin ($C_{21}H_{20}O_6$) is a major natural bioactive polyphenolic pigment extracted from turmeric contains the following physicochemical attributes:

1. Chemical structure of curcumin
2. Vogel first discovered the curcumin in crystalline form (Vogel. and Pelletier., 1815) and recognized as 1, 7-bis (4-hydroxy-3- methoxyphenyl)-1, 6-heptadiene-3, 5-dione or diferuloylmethane.
3. Curcumin (2% to 5%), demethoxycurcumin (DMC) 1.4%, and bis-demethoxy curcumin (BDMC) 1.2% are collectively known as curcuminoids: a group of polyphenolic, fat-soluble pigments responsible of the bright yellow-orange colour of turmeric (Payton *et al.,* 2007).
4. Curcuminoids extract can be easily analysed, isolated and purified by a different chromatographic method such as preparative TLC, HPLC and column chromatography.
5. NMR studies have confirmed that β-diketone moiety of curcumin readily undergoes keto−enol tautomerization. According to Sanphui *et al.,* (2011) enol form shows solid-state polymorphism and strongly stabilized by hydrogen bonding which is asymmetric intermolecular in nature.
6. The yellow-orange crystalline powder of curcumin is practically insoluble in water and ether but soluble in ethanol, dimethylsulfoxide (DMSO), acetic acid and acetone. For biological experiments, stock solutions of curcumin are prepared in DMSO and DMF.

Table 2. Various applications of curcuma species

S.No.	*Curcuma* **Species (Vernacular Name); Country**	Part Used	Various Applications	References
1.	*C. aeruginos Roxb.* (kali haldi); India	rhizome	Treatment of skin disorder, respiratory diseases (cough, asthma and bronchitis), rheumatic pains, piles, dysentery and diarrhoea	Dessy *et al.,* (2019)
2.	*C. amada Roxb.* (Diggi, diggi-thegacu); Bangladesh	root	Treatment of impotency	*Ayati et al., (2019)*
	(Amba haldi); India and Nepal	rhizome	Strains, fractured bone, asthma and snake bite	*Ayati et al., (2019)*
3.	*C. angustifolia Roxb.* (Nauhaine-haldai); Nepal and (Tikhur) India	rhizome	As an antiseptic in cuts, wounds and to check bleeding	*Ayati et al., (2019)*
4.	*C. aromatica (Salisb*. Vanhaldi); India	whole plant	Blood purification, hysteria and intestinal disorder	*Ayati et al., (2019)*
5	*C.australasica* ; Australia	rhizome, flowers	Anti-inflammatory, used as ornamental	Rajkumari & Sanatombi (2017)
6	*C. caesia Roxb.* (Sammi-seng); Bangladesh	tuber	As an antidote after poisoning, in liver pain	Partha and Hossain (2007).
	(Kola haladhi); India	rhizome	stimulant, carminative, sprain treatment of dysentery and gout	*Ayati et al., (2019)*
7	*C. rhabdota Sirirugsa;* Thailand	flowers	Ornamental use	Nair (2019)
8	*C. longa;* Pakistan	rhizome	Treatment of pimples and wounds	*Ayati et al., (2019)*
	(yung-ba); Bhutan	rhizome	As an antidote, anti-inflammatory, antiseptic, and preservatives	*Ayati et al., (2019)*
	Nepal	rhizome	Strains, wounds, injuries as an anthelmintic, stimulant, tonic, jaundice, liver disorders and blood purifier.	*Ayati et al., (2019)*
	Philippines	rhizome	To treat arthritis, cuts and wounds	*Ayati et al., (2019)*
	Madagascar	eaves	For curing malaria and jaundice and it is also used in pregnancy	*Ayati et al., (2019)*
	(Shapi natiyu); Peru	rhizome	In bronchitis and malaria	*Ayati et al., (2019)*
	Colombia	rhizome	As a circulatory stimulant, body detoxification, healing wounds, strengthen the immune system, and as a condiment	*Ayati et al., (2019)*
9	*C. caesia,* (black turmeric); India	rhizome	treatment of haemorrhoids, inflammation, and menstrual disorder	Tamrakar & Arora (2019)

7. The insolubility of curcumin in water and neutral pH is due to the lipophilic nature of this polyphenol which can be explained by the log P between 2.3 and 3.2. At alkaline pH, the phenols are converted into phenolate ions and make it water-soluble.
8. Curcumin degrades rapidly at both neutral and alkaline pH, but quite stable in the acidic pH. Noteworthy that with decreasing pH the equilibrium shifts toward the neutral form (low/no solubility) of the molecule in parallel. That

is why in experimental conditions curcumin first dissolves in a polar protic organic solvent, then diluted with an excess of water.

9. The experimental observations like lipid membrane affinity, interactions with the hydrophobic pocket of proteins and blood-brain barrier crossing ability proves the hydrophobic nature of curcumin.
10. Curcumin is a photo-labile molecule and its recommended storage conditions are under low temperature (-20°C).
11. The limited photostability of curcumin and tendency to generate singlet oxygen upon excitation plays a vital role in biological properties of curcumin.

TEMPTATION OF THE CURCUMIN AS SOLID GOLD

Curcumin elicits great interest as a medicine, food additive and a dietary supplement within the ethnomedicinal tradition over millennia. Curcumin appears to have several attractive qualities from a drug discovery standpoint and as a result, it is declared as a medicinal herb by the World Health Organization (WHO, 1999). WHO declared the adequate daily intake of curcumin as a foodstuff additive in the range of 0–3 mg/kg. It is "generally recognized as safe" (GRAS) by Food and Drug Administration (FDA) and can be used as a food additive at levels up to 20 mg per serving and a healthy person can take up to 12 grams per day. Thus it is not essential to researchers for its approval as a therapeutic from regulatory agencies. A Google hit of the term "turmeric" results over 37 million links. In the last decade, approximately a hundred patents were filed each year, globally and about three hundred papers published regarding its biological activity and innovative formulations.

In India, the medicinal uses of turmeric, are known since the Vedic period. It was used as a culinary spice and had great religious significance. In herbal and traditional medicine, turmeric is used for various disorders and disease conditions listed in Table 2. Oppenheimer, (1937) reported first time the use of curcumin in human diseases. The multiple pharmacological activities and therapeutic potential against complex diseases makes it a versatile natural product and has gained considerable attention in recent years. Some researchers have trumpeted it for apparently being better than prescribed drugs for neurological disorders, cancer and diabetes. Now, it is available in organic supplements, especially in western countries.

Why a kind of weird-looking rhizome attracted all this interest? Well, this golden spice ingredient has been categorized as highly pleiotropic compound which can target wide range of cellular components at molecular level comprising gene expression factors, growth factors, chemo/cytokines and various enzymes related with cell proliferation and apoptosis mechanism. Numerous biological activities associated with curcumin listed as follow:

Antioxidant Activity

Curcumin directly hunts diverse groups of reactive oxygen/nitrogen-containing free radicals (ROS/RNS). The presence of phenolic groups in the structure of curcumin is responsible for its antioxidant activity. Curcumin not only inhibits several crucial ROS-generating enzymes such as lipoxygenase/cyclooxygenase and xanthine dehydrogenase/oxidase but up-regulate superoxide dismutase and glutathione peroxidase which are well known for antioxidant defence mechanism of the body through the activation of the nuclear factor E2-related factor 2 (Nrf2)-dependent pathway. Thus, boosting immunity is one of its substantial characteristics.

Anti-Inflammatory Activity

Due to antioxidant properties, curcumin has been specially recognized as prominent anti-inflammatory plant in nature. It inhibits the responsible mediators of the inflammatory action, including cyto/chemokines, adhesion molecules, growth factors and enzymatic pathways. The ability of curcumin to enhance antibody responses and modulate the immune system even in low concentration, would be the reasonable explanation of reported beneficial effects of curcumin against various inflammatory diseases such as arthritis, allergy and asthma, heart disease, neurodegenerative diseases such as Alzheimer's disease, metabolic disorder such as diabetes, and cancer (Singh, 2014).

The anti-inflammatory properties of curcumin arise from:

Inhibition of Nuclear Factor-Kappa B (NF-κB) Pathway

NF-κB is a crucial transcription factor plays an important role in cell proliferation and differentiation. It binds DNA and triggers the transcription of the COX-2 and other pro-inflammatory genes responsible for anti-inflammatory actions.

Inhibition of Pro-Inflammatory Pathways

The following pro-inflammatory pathways hit by the curcumin:

Mitogen-activated protein kinase (MAPK)
Janus kinase (JAK)/Signal transducer
Activation of transcription (STAT)-dependent signalling pathways

Anticancer Activity

The strain of anticancer activities of curcumin in different types of cancer is due to regulating different cell signalling pathways responsible for the proliferation and induction of apoptosis mechanism. Curcumin is well reported to inhibit tumour invasion and angiogenesis process. Curcumin also interacts with various biotransformation enzymes. It not only inhibits procarcinogenic bioactivation enzymes like cytochrome P450 (CYP) and COX-2, increases the activity of detoxification enzymes as well. On the basis of a comparative study of cancer prevalence in India and the U.S. carried out by the National Cancer Institute and the National Institutes of Health, the number of cases in different types of cancer, were much lower in India than in the U.S. because the frequent consumption of turmeric as a food spice in India.

Neuroprotective Activity

Neurodegenerative disorders like Alzheimer disease characterized by an abnormal accumulation of β-amyloid peptides (Aβ) and neurofibrillary tangles within the brain leading to progressive memory loss and cognitive dysfunctions. The pathological markers of AD are neurofibrillary tangles formed by aggregated Tau protein and neurotic plaques comprised of β-amyloid. Under normal conditions, Tau protein stabilizes microtubules in the cytoskeleton of neurons. However, in pathological conditions, Tau is abnormally hyperphosphorylated and no longer binds to microtubules, forming insoluble aggregates in the intracellular space of the neuron, disrupting the axonal transport, and inevitably resulting in neuronal death. Mitochondrial dysfunction, oxidative and inflammatory stress is some of the other changes occurring during AD in the brain.

Due to the multifactorial nature of the disease, a number of factors have to be taken care of while tackling AD. As a result of this multifactorial and heterogeneous nature of the disease, compounds with multiple properties are very good candidates for treating AD. Curcumin is such a versatile compound having a multitude of properties. Apart from the anti-amyloid properties and anti-tau hyperphosphorylation properties against the two major pathological changes in AD, curcumin is also able to regulate the secondary changes that occur during the disease like oxidative stress, inflammatory stress and cholesterol regulation which are very beneficial while considering AD therapy.

Anti-Diabetic Activities

Scientific literature has been well reported that curcumin boasts anti-diabetic effects and relieves diabetes complexity. The anti-diabetic potential of curcumin may be

cumulated as its potent ability to suppress oxidative stress and prominent anti-inflammatory activity. Further, it plays a crucial role in the endothelial dysfunction and down-regulation of cellular factors related to diabetes induction. In addition, curcumin formulation has been reported to reduce insulin resistance and improve glucose tolerance.

The Real Story: Is Versatile Curcumin Just Pyrite?

Turmeric, the golden spice has been used in Asia for centuries, now has a sterling reputation in western countries as a super-food. But a crucial open question which has attracted increasing attention in recent years that what is the directive force responsible for the multifunctional nature of curcumin? This question needs to be further addressed in detail.

Now take a look for another side of the coin, what's the real story? The curcumin as a wonder drug could not be so effective and safe has been proved on the basis of a plethora of evidence-based recent clinical trials and epidemiological studies. Unfortunately, such research findings are not published or in other words, often weren't communicated fairly in society. According to Nelson *et al.,* (2017), these actual research outcomes generally treated as folklore and true results don't really execute to what they're reported as. Further, in this chapter, to avoid such discrimination the negative aspects of curcumin reviewed. The main limitations are as follow:

Poor Pharmacokinetic Properties

It is a well-accepted fact that curcumin has poor pharmacokinetic properties which can be explained in terms of ADMET profile.

Absorption

Especially for oral administration, the absorption is a critical consideration of any potential therapeutic. Various studies have been reported using a wide variety of oral formulations of curcumin. Despite an oral dose approximately 12 g/day has no adverse effects and relatively well tolerated, in the majority of the experiments, the absorption of the compound in serum is negligible and not detectable. Surprising, the oral bioavailability of curcumin derivatives in the rat's serum has been reported less than 1%. To boost the absorption and bioavailability profile of the curcumin various formulations have been developed. Among them, nano and lipid dispersion based formulations and have been identified, with slight improvement in the curcumin bioavailability. Thus, in terms of reaching a target, apparently curcumin is not well absorbed from oral doses since it couldn't be detected in the blood

serum of participants of clinical trials-no matter how high the dose. It has been well established that absorbed curcumin gets quickly metabolized via enzymatic actions in the liver. Further, poor absorption of curcumin was also supported from the fact that a major concentration of an oral dose of curcumin sample in rodent sample was excreted through faeces.

Distribution

The impact and therapeutic utility of a compound can be decided by its degree of distribution in the body. The distribution studies of curcumin and its derivatives have only been less evaluated in humans and have been extensively studied in rodents. Several studies in animal models have indicated variable distribution patterns which mainly affected by tissue types. The differences in the preparation of the sample dose used in the study, differences in extraction, preparation, and detection methods of sample dose, and lack of specificity in the detection assay, are some possible reasons for a high degree variability in distribution patterns. Further literature suggests that curcumin is degraded and/or transformed before and/or after absorption and does not distribute to any specific organs in appreciable levels.

Metabolism

It has been reported that due to its reactive structure, any curcumin that is absorbed by the body has a high potential to be metabolized through both conjugation and reduction pathways in humans and rodents. Curcumin given orally undergoes conjugation, resulting in curcuminglucuronide and sulfates while administered systemically undergoes reduction to generate tetra-hydro curcumin, hexa-hydro curcumin and octa-hydro curcumin. Phase I metabolism primarily results in a reduction of the double bonds in the heptadienedione system, mainly through the action of alcohol dehydrogenase. Phase II metabolic processes rapidly conjugate 1 and its reduced metabolites. The most abundant conjugates are glucuronides and sulfates at the phenolic positions. Unsurprisingly, curcumin also interacts readily with glutathione in a nonenzymatic manner, presumably through a Michael-type addition.

Excretion

In multiple studies in rats demonstrated that when curcumin and its derivatives orally administered the majority of curcumin is excreted in the faeces. However, very little is detected in rodent urine while glucuronide and sulfate metabolites have been identified in rat plasma. In human models, there are conflicting reports about the excretion of curcumin and its metabolites.

According to Sharma *et al.,* (2001), patients with advanced colorectal cancer had been given 440–2200 mg/day of oral *curcuma* extract for up to 29 days but neither curcumin nor its metabolites were found in the plasma or urine of patients. They were only detectable in the faeces of these patients. Johnson Mukhtar, (2007), reported that curcumin or one of its metabolites was detected in the serum of one or three patients from each cohort of 12 or 15 patients, respectively.

Toxicology

Curcumin has shown broad reactivity against a number of human enzymes that are linked to compound toxicity, namely, hERG channels, cytochrome P450s, and glutathione S-transferase. The reactivity of each of these classes has important implications for potential toxic side effects: hERG channel inhibition is related to cardiotoxicity; cytochrome P450 (CYP450) and glutathione S-transferase (GST) inhibition can lead to impaired detoxification and potential toxic drug−drug contraindications. Beyond specific enzyme toxicity, curcumin has recently been shown to be an active iron-chelator *in vivo*, inducing a state of overt iron deficiency in mice fed diets poor in iron. Burgos-Morón *et al.,* (2010) reviewed that curcumin may cause toxicity under specific conditions and curcumin can cause a dose and time-dependent induction of DNA damage and chromosomal alterations both in vitro and in vivo at concentrations similar to those reported to exert beneficial effect. For a drug to be safe, it must also be devoid of long-term toxicity and the only fact that no major toxicity has been found in short-term studies in humans is not a proof of curcumin safety either.

Curcumin as Pan-Assay Interference Compounds (PAINS)

These are compounds that have been observed to show activity in multiple types of assays by interfering with the assay readout rather than through specific compound/target interactions. Curcumin exhibits all known PAINS-type behaviours such as covalent labelling of proteins, metal chelation,redox reactivity, aggregation,membrane disruption, fluorescence interference and structural decomposition.It may be concluded that any report of its activity in an assay that does not either exclude or account for these potential modes of assay interference should be treated with caution.

Curcumin as an Invalid Metabolic Panaceas (IMP)

Nelson *et al.,* (2017) reported that there have been over 120 clinical trials of curcumin and related compounds; but to date, not any successful double-blinded, a placebo-

controlled clinical trial has been reported. As a result, they have termed it an IMP - an "invalid metabolic panacea".

IMPS are invalid metabolic panaceas located inside the centre of the black hole of natural products that tend to exhaust research resources. IMPS are prototypes of improbable metabolic panaceas that show poor activity as a lead drug.

Chemical (In) Stability of Curcumin

Nelson *et al.,* (2017), reported that curcumin is an unstable drug candidate both *in vitro* and *in vivo* conditions. They quoted about it "A missile that continually blows up on the launch pad, never reaching the atmosphere or its intended target(s)."

Despite being highly effective against several human ailments, the therapeutic potential of curcumin is compromised. On intravenous administration, it disappears rapidly from the blood and quickly appears as metabolites in the bile. The poor bioavailability, resulting in sub-therapeutic concentration at the target site (Nelson *et al.,* 2017). Thus, none of the form of curcumin, or its derivatives, likely to acquire the necessary properties of good drug molecule i.e. chemical stability; high water solubility, potent and selective target activity, high bioavailability, broad tissue distribution, stable metabolism, and low toxicity".

CONCLUSION

The plethora of publications available on only the beneficial aspect of curcumin rather showing negative effects. This trend reflects that the benefit-side effect ratio of curcumin is shifted more towards the positive aspect only rather than its side effect and toxicity. This trend also keeps away the researchers with the state-of-the-art in the field. So in this direction, to establish the benefit-risk profile of curcumin and maintain its equilibrium unbiased future research is needed. Unfortunately, curcumin is regarded as efficient and safe in scientific literature without proving its efficiency and safety. In addition, the effectiveness of a drug is usually established by randomized, placebo-controlled, double-blind clinical trials, and no such trials have shown curcumin to be effective so far. Thus for unaware *researchers*, curcumin as a PAINS and IMP overture many tricky traps leads towards the false interpretation of the results of their experiments.

REFERENCES

Aggarwal, B. B., Surh, Y. J., & Shishodia, S. (Eds.). (2007). *The molecular targets and therapeutic uses of curcumin in health and disease* (Vol. 595). Springer Science & Business Media. doi:10.1007/978-0-387-46401-5_1

Ayati, Z., Ramezani, M., Amiri, M. S., Moghadam, A. T., Rahimi, H., Abdollahzade, A., & Sahebkar, A. (2019). Ethnobotany, phytochemistry and traditional uses of *Curcuma* spp. and pharmacological profile of two important species (*C. longa* and *C. zedoaria*): a review. *Current Pharmaceutical Design.*

Bao, W., Li, K., Rong, S., Yao, P., Hao, L., Ying, C., ... Liu, L. (2010). Curcumin alleviates ethanol-induced hepatocytes oxidative damage involving heme oxygenase-1 induction. *Journal of Ethnopharmacology*, *128*(2), 549–553. doi:10.1016/j.jep.2010.01.029 PMID:20080166

Bernardini, S., Tiezzi, A., Laghezza Masci, V., & Ovidi, E. (2018). Natural products for human health: An historical overview of the drug discovery approaches. *Natural Product Research*, *32*(16), 1926–1950. doi:10.1080/14786419.2017.1356838 PMID:28748726

Burgos-Morón, E., Calderón-Montaño, J. M., Salvador, J., Robles, A., & López-Lázaro, M. (2010). The dark side of curcumin. *International Journal of Cancer*, *126*(7), 1771–1775. PMID:19830693

David, B., Wolfender, J. L., & Dias, D. A. (2015). The pharmaceutical industry and natural products: Historical status and new trends. *Phytochemistry Reviews*, *14*(2), 299–315. doi:10.100711101-014-9367-z

Dessy, V. J., & Sivakumar, S. R. (2019). Clonal propagation of *Curcuma aeruginosa Roxb.*: A versatile medicinal plant. *Medicinal Plants-International Journal of Phytomedicines and Related Industries*, *11*(1), 67–72. doi:10.5958/0975-6892.2019.00008.X

Dias, D. A., Urban, S., & Roessner, U. (2012). A historical overview of natural products in drug discovery. *Metabolites*, *2*(2), 303–336. doi:10.3390/metabo2020303 PMID:24957513

Ghosh, S., Banerjee, S., & Sil, P. C. (2015). The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. *Food and Chemical Toxicology*, *83*, 111–124. doi:10.1016/j.fct.2015.05.022 PMID:26066364

Johnson, J. J., & Mukhtar, H. (2007). Curcumin for chemoprevention of colon cancer. *Cancer Letters*, *255*(2), 170–181. doi:10.1016/j.canlet.2007.03.005 PMID:17448598

Labban, L. (2014). Medicinal and pharmacological properties of Turmeric (*Curcuma longa*): A review. *International Journal of Pharma and Bio Sciences*, *5*(1), 17–23.

Nair, K. P. (2019). Genetics of Turmeric. In *Turmeric (Curcuma longa L.) and Ginger (Zingiber officinale Rosc.)-World's Invaluable Medicinal Spices* (pp. 37–51). Cham: Springer.

Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F., & Walters, M. A. (2017). The essential medicinal chemistry of curcumin: Miniperspective. *Journal of Medicinal Chemistry*, *60*(5), 1620–1637. doi:10.1021/acs.jmedchem.6b00975 PMID:28074653

Oppenheimer, A. (1937). Turmeric (curcumin) in biliary diseases. *Lancet*, *229*(5924), 619–621. doi:10.1016/S0140-6736(00)98193-5

Partha, P., & Hossain, A. E. (2007). Ethnobotanical investigation into the Mandi ethnic community in Bangladesh. *Bangladesh Journal of Plant Taxonomy*, *14*(2), 129–145. doi:10.3329/bjpt.v14i2.532

Patridge, E., Gareiss, P., Kinch, M. S., & Hoyer, D. (2016). An analysis of FDA-approved drugs: Natural products and their derivatives. *Drug Discovery Today*, *21*(2), 204–207. doi:10.1016/j.drudis.2015.01.009 PMID:25617672

Payton, F., Sandusky, P., & Alworth, W. L. (2007). NMR study of the solution structure of curcumin. *Journal of Natural Products*, *70*(2), 143–146. doi:10.1021/np060263s PMID:17315954

Rai, D., Kumari, G., Singh, A., & Singh, K. (2013). Curcuminbioconjugates: Studies on structure-activity relationship and antibacterial properties against clinically isolated strains. *Medicinal Chemistry (Shariqah, United Arab Emirates)*, *9*(7), 999–1005. doi:10.2174/1573406411309070014 PMID:23189999

Rajkumari, S., & Sanatombi, K. (2017). Nutritional value, phytochemical composition, and biological activities of edible Curcuma species: A review. *International Journal of Food Properties, 20*(sup3), S2668-S2687.

Ravindran, P. N., Babu, K. N., & Sivaraman, K. (2007). *Turmeric: the genus Curcuma*. CRC press.

Sanphui, P., Goud, N. R., Khandavilli, U. R., Bhanoth, S., & Nangia, A. (2011). New polymorphs of curcumin. *Chemical Communications*, *47*(17), 5013–5015. doi:10.1039/c1cc10204d PMID:21431190

Sarkar, A., Sarkar, D., & Poddar, K. (2019). Plant metabolites as new leads to drug discovery: approaches and challenges. Medicinal Plants: Chemistry, Pharmacology and Therapeutic Applications, 61.

Sharma, R. A., McLelland, H. R., Hill, K. A., Ireson, C. R., Euden, S. A., Manson, M. M., & Steward, P. (2001). Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clinical Cancer Research*, *7*(7), 1894–1900.

Singh, R. K. (2014). *Therapeutic Uses of Curcumin Spice*. Academic Press.

Tamrakar, V., & Arora, C. (2019). Curcuma caesia: Present status and future prospect as herbal drug. *Progressive Agriculture*, *19*(2), 258–261. doi:10.5958/0976-4615.2019.00036.X

Vogel, H. A., & Pelletier, J. (1815). Curcumin-biological and medicinal properties. *Journal of Pharmaceutics*, *2*(50), 24.

World Health Organization. (1999). *WHO monographs on selected medicinal plants.* WHO.

Chapter 13
Antioxidative Agents From Medicinal Plants

Sandeep Kumar
https://orcid.org/0000-0002-7576-9696
National Dairy Research Institute, India

Ahmad Hussain
https://orcid.org/0000-0002-1603-0154
National Dairy Research Institute, India

Manish Singh Sansi
National Dairy Research Institute, India

Daraksha Iram
National Dairy Research Institute, India

Priyanka
Indian Institute of Technology, Delhi, India

Ashutosh Vats
National Dairy Research Institute, India

ABSTRACT

The medicinal plants have been used by humans since ancient times, and the great civilizations of the world in ancient times were well aware of the benefits brought by the use of medicinal plants. This chapter provides important information regarding medicinal plants that have a wide variety of antioxidative agents ranging from bitter compounds that stimulate digestion system, phenolic compounds for antioxidant and numerous other pharmacological properties, antibacterial, and antifungal to tannins that act as natural antibiotics, diuretic substances, alkaloids, and so forth.

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INTRODUCTION

Medicinal plants are utilized by humans since history and also the great civilizations of the world were well aware of their use. However, the use of medicinal plants keeps on increasing after understanding their detailed functions and the components present in them. The use of medicinal plants were used by adding plant parts or extracts as additives in different types of foods and various herbal drinks for enhancing their effectiveness. Antioxidants are the substances which act against oxidative reaction. Within the biological systems, the antioxidant is the biological active molecule that is capable of preventing a precise oxidation reaction catalyzed by enzymes or a material which reacts with oxidizing agents before it causes oxidative damage to the other molecules.

Antioxidants even in trace amounts can stop or pause the oxidation process of easily oxidizable biomolecules present in the cell (Brewer, 2011). Free radicals are generated in the form of reactive oxygen species within the living organisms by completely different biochemical and physiological pathways has been observed, however, increased production of those may result in toward the progress of various diseases (Halliwell, 2007). Reactive oxygen species generation is necessary for many physiological processes e.g. cell proliferation, differentiation and programmed pathway for death of cell. They are intermediates of many important signaling processes; however, they are also toxic byproducts of normal metabolism (Mittler, 2017).

Reactive oxygen species are generated by the incomplete reduction of environmental oxygen (O_2) i.e., by excitation of oxygen to reactive half singlet oxygen (O_2^1) or by the transfer of electrons to oxygen which in turn forms superoxide radical (O_2^-), hydroxy radical (HO^-) or hydrogen peroxide (H_2O_2). Reactive oxygen species can cause oxidation of cellular organelles and results in the destruction of cells and tissues by oxidative processes (Asada & Takahashi 1987).

We have identified many potential sources of ROS generation in plants. Some of them are the normal reactions going down within the cell and concerned in normal metabolisms, such as respiration and photosynthesis. Reactive oxygen species may also be created by alternative factors like pathways increased throughout abiotic stress e.g. glycolate oxidase enzyme in peroxisomes during the process of photorespiration. Few new sources of reactive oxygen species generation have been identified in plants e.g. amine oxidases, peroxidases bounded to cell wall, and NADPH oxidases. These processes are tightly regulated and participates in reactive oxygen species generation during apoptosis and defense from pathogen (Asada & Takahashi, 1987).

The medicinal plants are simply accessible and great supply of antioxidative compound as they contains a blend of various chemical substances that can demonstrate individually or unitedly to fix health problems and improvement in diseases. Indeed,

a solitary plant might have a decent variety of phytochemical compounds starting from phenolic compounds as antioxidant and bitter compounds which stimulates digestion, also and various alternative medicinal properties, antifungal, antibacterial, diuretic substances tannins that act as naturally occurring antibiotics, and, alkaloids, and so forth (Miguel, 2010). In the body, antioxidative agents decrease the hazard of degenerative ailments emerging due to oxidative pressure. The antioxidative agents can be of different types based on sources i.e. primary antioxidative agents and secondary antioxidative agents present in the nature. The primary antioxidants are those that counterbalance reactive oxygen species through a single electron transfer system or by either donating a hydrogen particle. On the opposite hand, secondary antioxidants are biological compounds that have the ability to neutralize pro-oxidant catalysts. These include chelators which bind tightly to pro-oxidant metalic ions such as copper and iron, demonstrated by citric acid (CA) and ethylenediaminetetraacetic acid (EDTA). Other antioxidants can neutralize reactive oxygen species like singlet reactive oxygen (e.g. beta-carotene) and prevents its deteriorating effects (Barry, 1999).

We have a variety of artificially synthesized antioxidants that can be used to capture free radicals or regulate oxidative processes such as propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, and tertbutylhydroquinone etc. Because synthetic antioxidants at higher concentrations can cause cytotoxic and cancerous effects on animals, therefore recent research interest has targeted on natural antioxidants from medicinal plants. These natural antioxidants are very significant in reducing the risk of certain diseases and providing health benefits (Shahidi *et al.,* 1992). So we can say that an antioxidant interferes with different pathways and diminishes localized reactive oxygen concentration and pause chain reaction by scavenging generation of free radicals or by destroying free radicals or peroxides into water or less reactive species (Miguel, 2010). Recently, the natural antioxidative agents have pulled insignificant consideration of public and researchers to a great extent because of adverse pharmacological observation of various synthetic antioxidants and developing mindfulness amongst the users (Ramalakshmi *et al.,* 2008).

This is demonstrative of the way that in the recent year's exploration on antioxidative agents and medicinal plants has increased tremendously. Keeping all these points in mind the current chapter focuses on (i) introduction to antioxidants, reactive oxygen species and functions of antioxidants (ii) natural and synthetic antioxidants in the medicinal plants; (iii) major categories of antioxidants in medicinal plants (iv) medicinal/traditional use of antioxidants in drugs or for specific function.

NATURAL AND SYNTHETIC ANTIOXIDANTS

We have mainly two types of antioxidants: a majority of them extracted directly from plants are called natural antioxidants while others are produced by chemical methods in industries or synthetic in nature. The two types of antioxidative agents are described below.

Natural Antioxidants

The natural antioxidative compounds have been grouped into two main class i.e. enzymatic antioxidants and non- enzymatic antioxidants. Medicinal plants offer a broad choice of natural antioxidants that are unique in their physical properties, chemical properties, structural arrangement and chemical composition, and place of action (e.g. flavonoids, phenolics, carotenoid's, anthocyanins, terpenoids, ascorbic acid, tannins, tocopherols, etc. Among these antioxidants, flavonoids and phenolics have been reported as the most powerful natural antioxidants and systematically protecting the cells by hunting of reactive free oxygen species (superoxide anion, hydroxyl radical, peroxynitrite, peroxyl radicals, and hypochlorous acids) in different cellular models (Halliwell, 2007). Various types of antioxidants that have been reported in medicinal plants are polyphenols, glutathione, α-lipoic acid, thioredoxin, ascorbic acid, vitamin-A, coenzyme-Q, α-tocopherols melatonin, β-carotenoids, and antioxidative enzymes such as SOD, catalase, glutathione-S-transferase, glutathione peroxidase, and glutathione reductase etc. All of these antioxidants have been widely investigated and found to be very helpful in the amelioration of oxidative stress and prevention or treatment of diseases resulting from damage mediated by oxidative stress (Ighodaro & Akinloye, 2018).

We have described major antioxidants, types of antioxidants and the functions of antioxidants in the tabular form below (table-1) for more understanding related to: (a) the sources of natural antioxidants, (b) the components present in natural antioxidants, (c) mode of action of various natural antioxidants (Pratt, 1992).

Natural Sources of Antioxidants

Some of the vital sources of antioxidants are olives, oilseeds, amla, orange, citrus poly and peel, cocoa powder or shell, plant (extracts), protein hydrolysate, heated products, resins, microbial products, herbs and spices, oat flour, soy products, tempeh, algae, etc. These sources of antioxidants from various plants are utilized for isolation/extraction and purification of antioxidants for medical or pharmacological applications. The main components present in the antioxidants are amino acids, other organic acids, carotenoids, ascorbic acid, flavonoids, peptides, tannins, tocopherols,

melanoidin, etc. which makes them good for use in medical and other applications. Some of the antioxidative compounds present in medicinal plants along with their mechanism of action of various natural type of antioxidants are shown in table 1.

Table 1. Major antioxidative agents found in the medicinal plants and the mechanism by which various natural antioxidants acts in the cell or body

Compound name	Mechanism of action
Alkaloids	Show cytotoxicity against tumour cell lines and Inhibit the activity of topoisomerase I and II.
Phenolics	Hydrogen atom donated by phenolic compounds to the free radicals cause inhibition of oxidative process of lipids, fats, and proteins.
Catechins	Enhanced SOD and catalase activity.
α-Tocopherol	Lipid peroxide radicals scavenges free radicals by the transfer of hydrogen.
Carotenoids	It is physical quenchers of reactive oxygen species
Tannins	Relaxes vascular segments pre-contracted with norepinephrine and can increase the production of nitric oxide

TYPES OF ANTIOXIDATIVE AGENTS IN MEDICINAL PLANTS

We have a wide variety of antioxidative agents or compounds which are involved in various functions in the body. Some of the major antioxidants found in medicinal plants e.g. phenolics, flavonoids, tannins, carotenoids, vitamins and minerals are described below:

Phenolic Compounds

Phenolic compounds are biologically active secondary metabolites present in the medicinal plants that are derivatives from the shikimic acid, phenylpropanoid, and pentose phosphate pathways. Phenolic compounds are the essential part of human diet that acts at molecular level (Randhir *et al.,* 2004). The phenolic compounds are of significant interest to the researchers because of their abundant natural antioxidant properties. the most important sources of phenolic compounds within the human diet are vegetables, fruits, and beverages Phenolic compounds comprise of many different groups of compounds e.g. flavonoids, phenolic acids, glycosides and anthocyanins etc. Phenolic compounds possess an aromatic ring containing hydroxyl groups and the structures may vary from a simple phenolic acid molecule (e.g. gallic acid, vanillin, caffeic acid), to complex high-molecular-weight biomolecules such

as polyphenols (flavonoids, stilbenes) and the polymers derived from these varied groups (Andersen & Markham, 2005).

The sole determinant of the antioxidant activity of phenolic compounds is the position and number of the hydroxyl groups present in the simple phenolic structure and the type of substitutions in the aromatic rings. Formation of phenolic compounds and polyphenolics in the plants takes place through the shikimic acid pathway. Tyrosine and phenylalanine act as the precursors to all the phenolic compounds. By the action of enzymes, phenylalanine ammonia-lyase (PAL) or tyrosine ammonia-lyase (TAL), an ammonia molecule from either of these amino acids is removed respectively. This leads to the formation of p-coumaric acid and trans-cinnamic acid molecules. Hydroxybenzoic acid predominates in grains, cereals, and legumes. Their formation takes place from the latter class of compounds by loss of a two-carbon moiety. Furthermore, coumaric acid reacts with coenzymes to form carbaryl coenzyme A, which in turn reacts with three molecules of malonyl coenzyme A and results in the formation of chalcones that can give rise to different subclasses of flavonoids (Shahidi, 2015).

Flavonoids

Flavonoids are a low molecular mass class of biological entities that forms more than 1/2 of the natural 8000 different types of phenolic compounds. They are 15- carbon atoms, arranged in a C6–C3–C6 conformation (Waterman, 1993). Basically flavonoids structure contains two aromatic rings (A and B rings) which are linked by 3 carbons that are generally in the oxygenated central pyran ring, or heterocyclic C ring. The first aromatic ring is derivative of the malonate pathway, while the second aromatic ring is resultant from the shikimic acid pathway (Merken & Beecher 2000). Different types of substitutions in ring C ends up in the formation of major flavonoid categories i.e. flavones, flavonols, flavanones and flavanonols, flavanols, anthocyanins, chalcones, isoflavonoids, neoflavonoids and biflavonoids (these are dimers of flavones, flavonols, and flavanones). Out of these, flavonols and flavones are two most commonly, naturally occurring, structurally different groups of flavonoids (Hollman & Katan, 1999). Different types of substitutions mainly include alkylation, oxygenation, acylation, glycosylation, and sulfation (Pietta, 2000).

Naturally occurring and different types of flavonoids are present in the conjugated or free forms in the medicinal plants. they're the most important class of phenolics within the dietary spices and medicinal herbs (Huang *et al.,* 2008).

Flavonoids are generally present as glycosides and contains attached sugar groups or more sugar groups linked through carbon-carbon bonds or by O-glycosidic bond (O-glycosides) or, but some flavonoids are without *O*-glycosidic bond (Cai *et al.,* 2006). Over 80 totally different sugar moiety have been reported to attached with

*Table 2. **C**ategories of different phenolic compounds in medicinal plants. The basic structure of phenolic compounds is six carbon while in complex phenolic compounds increasing carbon units are present which provides structural complexity to the phenolic compounds (Balasundram et al., 2006)*

Structure	Type
C_6	Simple phenolics and benzoquinones
C_6-C_1	Hydroxybenzoic acids
C_6-C_2	Phenylacetic acids and acetophenone
C_6-C_3	Hydroxycinnamic acids, chromenes, chromones phenylpropanoids (coumarins and isocoumarins
C_6-C_4	Napthoquinones
C_6-C_1-C_6	Xanthones
C_6-C_2-C_6	Anthraquinones and stilbenes
C_6-C_3-C_6	Flavonoids and isoflavonoids
$(C_6$-$C_3)_2$	Neolignans and lignans
$(C_6$-C_3-$C_6)_2$	Biflavonoids
$(C_6$-$C_3)_n$	Lignins
$(C_6$-C_3-$C_6)_n$	Condensed tannins such as flavolans and proanthocyanidins

flavonoids such as glucoside, galactoside, apiosylglucoside, glucuronide, rhamnoside, arabinoside, and malonyl (Hollman & Arts, 2000).

Tannic Acid (Tannins)

Tannins are polyphenolic biological compounds having molecular weight range from 500 to 4,000. Tannic acids are naturally occurring, water-soluble compounds and usually classified into two types: hydrolyzable tannic acid (gallo- and ellagi-tannins) and condensed tannic acid (proanthocyanidins) (Cai *et al.,* 2004). The basic unit which form hydrolyzable tannins is gallic acid and its derived compounds (Fresco *et al.,* 2006). The hydrolyzable tannins are the complex polyphenols, which upon degradation release sugars and phenolic acids. Their complex bonds can be degraded through either enzymatic and non-enzymatic hydrolysis or extreme of pH changes. The hydrolyzable tannins have a central core made from polyhydric alcohols like aldohexose and hydroxyl groups, that are part or entirely esterified by gallic acid referred to as gallotannins or by hexahydroxy-diphenic acid or different substituents (e.g., chebulic acid) (ellagitannins), etc. (Cai *et al.,* 2006). The condensed tannic acid represent higher structural complexity and more widespread distribution in the medicinal plants as compared to hydrolyzable tannic acid. They're mainly the oligo

and polymers of flavan-3-diols (e.g. epicatechin or catechin derivatives), which also referred as proanthocyanidins (Schofield *et al.,* 2001). It has been reported by some authors that the polymers of flavan-3,4-diols are also a member of condensed tannins class known as leucoanthocyanidins (Cai *et al.,* 2006). Complex tannins are made up of simple units of catechin joined to ellagitannin or gallotannin, minimum of two gallic acid units linked by carbon-carbon bond surrounds the core. The most powerful antioxidants that are commonly used in cancer and health care treatment are oligomeric proanthocyanidins, that are present in grape seed, skin and bark of pine (Huh *et al.,* 2004).

Carotenoids

Carotenoids are one amongst the predominantly distributed class of pigments present in the nature. Around 1178 known naturally occurring carotenoids have been recorded from 700 organisms and new carotenoids are keep on adding in the list annually (Yabuzaki, 2018). Carotenoids are a category of hydrocarbons (carotenes) and other are their oxygenated form (xanthophylls). Generally, carotenoids are made of polyene chains and contain 9-11 double bonds and probably terminate in a ring. Carotenoids are 40 carbon atoms organic molecule derived from 4 terpenes. Carotenoids are classified basis of the number of C- atoms (C-30, C-40, C-45, and C-50) that constitute the structure of carotenoids, but only the forty carbon (C-40) carotenoids are profoundly present in nature. Carotenoids are synthesized by an organism such as cyanobacteria, some bacteria, plants, algae, and some fungi but not made by animals (Yabuzaki, 2017). A carotenoid (C-40) after shortening by the removal of small fragments from either single or both ends is called as an apocarotenoid.

Over 100 unique naturally occurring apocarotenoids have been reported in nature and shows structural and functional diverse properties (Beltran & Stange, 2016). Some precursor molecules like Lycopene, β-carotene, and zeaxanthin are the precursors and responsible for the synthesis of apocarotenoids e.g. abscisic acid, strigolactone, bixin, crocetin and mycorradicin (Baba *et al.,* 2015). These carotenoid derived compounds are formed either via enzymatic or nonenzymatic oxidative cleavage of carotenoids (Saini *et al.,* 2015). Formation of carotenoids carried out by enzymes: carotenoid cleavage dioxygenases (CCDs), which catalyzes cleavage of carotenoids at specific double bonds and acts by adding single oxygen atoms to the adjacent carbon atoms alongside carotenoid backbone. Conversely, singlet oxygen attack, mainly on β-carotene takes place in the nonenzymatic way of apocarotenoid formation (Hou *et al.,* 2016).

Carotenoids pigments such as α- & β- carotene, γ-carotene, phytoene, lycopene, zeaxanthin, phytofluene, astaxanthin, lutein, β-cryptoxanthin, and fucoxanthin

have been reported for the beneficial properties mainly because of their functions as antioxidants. They have been recorded for providing beneficial effects in several diseases, like cardiovascular, and vision, tumor formation, immune response, regulation of gene expression related with cell-to-cell communication, provitamin A activity, and modulation of lipoxygenase activity (Merhan, 2017).

Terpenes

Terpenes are made of unsaturated hydrocarbons units derived from isoprene units. The isoprene unit has two conjugated double bonds in the structure and the chemical formula is CH2═C(CH3)─CH═CH2 (Pattanaik & Lindberg, 2015). Terpenes are polymerized forms of 5-carbon isoprene molecules (Ahrazem *et al.,* 2016). Terpenes are classified according to the number of isoprene units, such as 1-isoprene unit (5C), 2-isoprene units (10C), 3-isoprene units (15C), 4-isoprene units (20C), 5-isoprene units (25C), 6-isoprene units (30C), and 8-isoprene units (40C) and referred as hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes (squalene), and tetraterpenes (carotenoids) respectively. We also have polyterpenes made up of high number of isoprene units (Varma, 2016). Monoterpenes, sesquiterpenes, diterpenes, and sesterterpenes shows head-to-tail joining of isoprene units; while triterpenes and tetraterpenes (carotenoids) shows head-to-head joining of isoprene units (Iriti *et al.,* 2009).

The most important group of terpenes are carotenoids with the C40H64 molecular formula and formed by a tetraterpene; 8-isoprene units (Wagner & Elmadfa, 2003). Carotenoids are orange, red, and yellow colored pigments and present in the fruits, vegetables and in all green leafy vegetables. Colors shown by carotenoids vary from dark red to light yellow and their properties are similar to lipids such as solubility in oils and organic solvents (Gómez-García & Ochoa-Alejo, 2013). Two molecules of geranylgeranyl- PP by condensation forms carotenoids (Iriti *et al.,* 2009). The first carotenoid known as phytoene formed by prephytoene diphosphate and it is found linked with the chlorophyll in the green plants. Phytoene synthase is the key enzymes in this first stable carotenoid synthesis reaction. Phytofluene is the second product of carotenoid biosynthesis pathway that is formed by the action of phytoene desaturase and result in the formation of saturated double bonds. Finally, three types of carotenes (α, β, & γ) are produced from lycopene molecule by the action of lycopene cyclase. α & β-carotenes are the products of hydroxylation reaction catalyzed by the β-carotene hydroxylase (Kopsell & Kopsell, 2006).

Ascorbic Acid (Vitamin-C)

Ascorbic acid (AA) or vitamin-C rich diet is an essential part of human diet and must be consumed for survival and continuation of normal body functions. Ascorbic acid is the water-soluble antioxidant. It's a reducing agent that itself gets oxidized, and prevents other molecules from oxidation. This is the most significant attribute of vitamin-C, which is responsible for all of its identified functions. Imbalance in the antioxidants in tissues partly leads to many disorders such as cancer and atherosclerosis (Padayatty *et al.,* 2003). Role of ascorbic acid (AA) or vitamin-C can be associated to cancer treatment, because higher doses of vitamin-C can cause an increase in the survivability of cancer patients approximately four times (Cameron & Pauling, 1976). However, these results could not be repeated in other in vivo studies performed by oral feeding of vitamin-C (Creagan *et al.,* 1979). Ascorbic acid has been proved to boost the immune system and self-defense within the body. Ascorbic acid can increases the phagocytes by chemotaxis and thus enriches the microbicidal potential of the body.

Ascorbic acid is a lactone and contains six-carbon (cyclic carboxylic esters). Ascorbic acid is synthesized from glucose in the liver by the most mammalian species, however humans, guinea pigs and some of the primates cannot synthesize this because these organisms lack the enzyme gulonolactone oxidase (product of GULO-gene), required for the synthesis of ascorbic acid from precursor molecule (Nishikimi *et al.,* 2011).

Some antioxidant systems (vitamins and minerals) with their active component and location in the cell and the molecular functions performed by the antioxidants have been summarized in table 3.

Synthetic Antioxidants and Their Drawbacks

The medicinal applications of synthetic antioxidants and their application makes them more attractive in industries like preservatives in the food and cosmetic industry. Generation of free radicals is liable for lipid peroxidation and are the major causal factor in decay of food substances during storage or processing in the food industries, (Chen & Ho, 1997). Synthetic antioxidants such as propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, and tertbutylhydroquinone, ethoxyquin, metabisulfite, and tertbutylhydroquinone etc. are widely applied in the dairy and food industry as a replacement of primary antioxidants that can capture free radical generation and then the oxidation reaction and off-flavor development can be checked. The toxicological and nutritional studies showed that the use of these synthetic antioxidants is harmful and toxic to human being, therefore use of

Table 3. Some antioxidant systems (vitamins and minerals) with their active component and location in the cell and the molecular functions performed by the antioxidants (Dulal et al., 2019).

Vitamins/minerals (antioxidants)	Functions	Component (location in cell)
Vitamin C	It reacts with numerous types of reactive oxygen/nitrogen species (ROS/RNS)	Ascorbic acid (Cell cytoplasm)
Vitamin E	Halts fatty acid peroxidation chain reactions.	α-tocopherol (Cell membranes)
β-carotene	It has been shown to prevent the initiation of fatty acids peroxidation and stops chain reaction	β-carotene (Cell membranes)
Copper	It is an antioxidant protein which can prevent copper or irons involvement in the oxidation reactions	Ceruloplasmin (Water phase)
Iron	This enzyme found in liver and changess hydrogen peroxide (H2O2) to water (H2O)	Catalase (Cell cytoplasm)
Copper and zinc	This enzyme helps to conversion superoxide form of ROS to the hydrogen peroxide	Superoxide dismutase
Manganese and zinc	It converts superoxide into hydrogen peroxide.	Superoxide dismutase
Selenium	Hydrogen peroxide converts to water by this enzyme.	Glutathione peroxidase

these artificially synthesized antioxidants has started to be restricted and substituted by natural antioxidants (Imaida *et al.,* 1983).

MEDICINAL PLANTS AND ANTIOXIDANTS

Detailed information regarding important medicinal plants, their scientific names, family, medicinally used parts, the antioxidative compounds present in them, their medicinal use or traditional use and mechanism of action can be obtained below from the table-4.

CONCLUSION

In conclusion, we can say that the medicinal plants are natural, abundant and easily available supplier of antioxidants because they contains a blend of diverse chemical substances that have demonstrated the ability to fix disease and improve health. Free radicals are generated by many factors, some of them are the biochemical reactions takes place in the cell, also different types of abiotic and biotic stress. Antioxidants

Table 4. Important medicinal plants, their scientific/common names, family, medicinally used parts, the antioxidative compounds present in them, their medicinal use or traditional use or mechanism of action

Scientific name	Family	Medicinally used parts	Mechanism of action/ antioxidative compounds/ medicinal use	References
Zingiber officinale Roseoe	Zingiberaceae	Rhizome	Astringent, anti-inflammatory, antioxidant, anticancer, analgesic, antipyretic	Surveswaran *et al.,* (2007)
Geranium sanguineum L.	Geraniaceae	Root	Catechins, proanthocyanidines, tannins, and flavonoids,	Sokmen *et al.,* (2005)
Mentha spicata	Laminaceae	Leaf	Antiinflammatory, antiulcerogenic, and antioxidant,	Arumugam *et al.,* (2008)
Acacia auriculiformis Cunnex Benth	Fabaceae	Bark	Triterpenoid saponins, and tannins	Singh *et al.,* (2007)
Nardostachys jatamansi (D.Don) D.C.	Valerianaceae	root	Phenolic antioxidants have anticholinesterase activity	Ahmed *et al.,* (2009)
Artemisia capillaris Thunb	Compositae	Seedling	Caffeic acid, phenolic acids, coumarins and chlorogenic acid	Cai *et al.,* (2004)
Rheum ribes L.	Polygonaceae	Stem and roots	5-desoxyquercetin, and quercetin-3-*O*rhamnoside, chrysophanol, physcion, emodin, and quercetin,	Öztürk *et al.,* (2007)
Teucrium polium L.	Lamiaceae	Aerial parts	4',7-dimethoxy apigenin, 3',6-dimethoxy apigenin, apigenin and rutin	Sharififar *et al.,* (2009)
Prunella vulgaris L.	Labiatae	Inflorescence	Phenolic acids, tannins, flavonols, caffeic acid, anthocyanins and cyanidin	Cai *et al.,* (2004)
Thymus vulgaris (van ajwayan)	Lamiaceae	Whole plant	It causes free radical scavenging and increases the antioxidant acivity	Surveswaran *et al.,* (2007)
Diospyros abyssinica Hier	Ebenaceae	root bark	Lupeol, triterpenoids, betulin, and betulinic acid	Maiga *et al.,* (2006)
Caesalpinia sappan Linn.	Leguminosae	heartwood	Tannins, flavonols (quercetin), chalcones,	Cai *et al.,* (2004)
Bidens pilosa Linn.	Asteraceae	flowers and leaves	Pinene, cis and trans-ocimene, limonene, bourbonene, muurolene, cubebene, elemene, caryophyllene oxide, caryophyllene, megastigmatrienone and terpenes, etc.	Deba *et al.,* (2013)
Terminalia bellirica (Gaerth) Roxb.	Combretaceae	fruit	Tannins inhibits lipid peroxidation also scavenges reactive oxyegn in the rat liver microsomes and also inhibits the formation of intestinal ulcer and shown to exhibit a cytoprotective effect in the stomach mocosa	Sabu & Kuttan, (2009)
Morus alba Linn.	Moraceae	fruit	Stilbenes (oxyresveratrol), flavonols (rutin),	Cai *et al.,* (2004)
Salvia officinalis Linn.	Lamiaceae	aerial parts	Ferulic acid, rosmarinic acid, 3- and 5-caffeoylquinic acid; luteolin-7-glucoside, caffeic acid, 4',5,7,8tetrahydroxyflavone, apigenin-7-glucoside, flavonoids, phenolic acids, etc.	Lima *et al.,* (2007)
Stemona sessilifolia (Miq.)	Stemonaceae	root	Not identified	Cai *et al.,* (2004)
Phyllanthus emblica Linn.	Euphorbiaceae	fruit	It scavenges free radicals and reduced antioxidant activity.	Poltanov *et al.,* (2009)
Rauwolfia serpentina (sarpgandha)	Apocynaceae	stem	Antioxidant and free radical scavenging property.	Surveswaran *et al.,* (2007)
Rheum officinale Linn.	Polygonaceae	root	Phenolic acids such as gallic acid, anthraquinones (e.g. chrysophanol, emodin, physcion, rhein and their glycosides), hydrolyzable tannins, etc.	Cai *et al.,* (2004)
Mentha arvensis Linn.	Lamiaceae	leaf	Plant extract and essential oil showed radical scavenging and antioxidant activity.	Bhatt *et al.,* (2013)
Origanum vulgare Linn.	Lamiaceae	whole plant	It have antioxidant and free radical scavenging activity.	Surveswaran *et al.,* (2007)
Aconitum kusnezoffii Reichb	Ranunculaceae	root	Not identified	Cai *et al.,* (2004)
Ocimum basilicum Linn.	Lamiaceae	Leaf	It have antioxidant and free radical scavenging activity.	Aqil *et al.,* (2006)
Ocimum sanctum Linn.	Lamiaceae	whole plant, seed	It have antioxidant and free radical scavenging activity.	Gupta *et al.,* (2006)
Evolvulus alsinoides	Convolvulaceae	whole plant	Inhibition of lipid peroxidation and ABTS scavenging activity.	Auddy *et al.,* (2003)
Viola yedoensis Linn.	Violaceae	whole plant	p-coumaric acid), flavonols (kaempferol glycosides, Phenolic acids (p-hydroxybenzoic acid).	Cai *et al.,* (2004)

continued on following page

Table 4. Continued

Scientific name	Family	Medicinally used parts	Mechanism of action/ antioxidative compounds/ medicinal use	References
Curcuma longa Linn.	Zinziberaceae	Rhizome	Prostate cancer, stomach papilloma, leukemia, hepatoprotective, fibrosarcoma, antidiabetic, hypo-lipidemic cardiotonic and active against colon, bladder, liver, esophagus cancer	Ramadan *et al.,* (2011)
Murraya koenigii L. (Sprengel)	Rutaceae	Leaf	Ascorbic acid and phenolics possess powerful antioxidant and freeradical scavenging properties.	Gupta & Prakash, (2009)
Citrus aurantium Linn.	Rutaceae	Immature fruit	flavanones (hesperidin, naringenin, naringin)	Cai *et al.,* (2004)
Ficus microcarpa Linn.	Moraceae	bark, fruit and leaves	Phenolic compounds (vanillin, syringol, protocatechuic acid, and catechol), triterpenoids (friedelin, lupenyl acetate, epifriedelinol, glutinol, amyrin and amyrin acetate).	Kuo & Li, (1997)
Dracocephalum moldavica Linn.	Lamiaceae	aerial parts	Caffeic acid, luteolin-7-*O*-glucoside, luteolin, apigenin, rosmarinic acid, and ferulic acid.	Dastmalchi *et al.,* (2007)
Curculigo orchioides Gaertn.	Hypoxidaceae	Rhizome	Antioxidant radical and scavenging activity.	Surveswaran *et al.,* (2007)
*Uncaria tomentosa (Willd.*exSchft) DC.	Rubiaceae	Bark	Alkaloids (,speciophylline, uncarine, isomitraphylline mitraphylline, isoteropodine); quinoic acid,, polyhydroxylated triterpenes and glycosides	Pilarski *et al.,* (2006)
Leea indica (Burm.f) Merr.	Vitaceae	whole plant	Farnesol, esters of phthalic acid, gallic acid, ursolic acid, beta-sitosterol, lupeol, phthalic acid, palmitic acid, 1-eicosanol, and, solanesol etc.	Saha *et al.,* (2004)
Solanum nigrum Linn.	Solanaceae	aerial parts	Phenolic acids (chlorogenic acid)	Cai *et al.,* (2004)
Crataeva nurvala Buch-Ham.	Capparaceae	stem bark	Terpenoids (saponin, friedelin, phragmalin triacetate, diosgenin, tannin and lupeol, etc.)	Kumari & Kakkar, (2008)
Camellia sinensis Kuntza	Brassicaceae	Leaf	Antioxidant and Radical scavenging activity; in heart and lung diseases catechins are useful.	Surveswaran *et al.,* (2007)
Angelica sinensis (Oliv.) Diels	Umbelliferae	Root	Phenolic acids (ferulic acid), simple phenols (vanillin, p-cresol)	Cai *et al.,* (2004)

are the substance that are capable of preventing or neutralizing the oxidation reactions or reacts with oxidizing agents before it causes oxidative damage to the other molecules. We have diverse type of natural and synthetic antioxidants that are being used to capture the free radicals and regulate the oxidative process. However, it has been reported by some research groups that, exposure to higher concentrations of synthetic antioxidants may result in toxicity and carcinogenicity to the animals. Therefore, this chapter has focused on various kind of natural antioxidative agents present in the medicinal plants such as phenolic compounds, flavonoids, ascorbic acid, tannic acid, and carotenoids, etc.

REFERENCES

Ahmed, F., Chandra, J., & Res, A. U.J. P., & U. (2009). In vitro antioxidant and anticholinesterase activity of *Acorus calamus* and *Nardostachys jatamansi* rhizomes. *Journal of Pharmacy Research*, *2*(5), 830–833.

Ahrazem, O., Gómez-Gómez, L., Rodrigo, M. J., Avalos, J., & Limón, M. C. (2016). Carotenoid cleavage oxygenases from microbes and photosynthetic organisms: Features and functions. *International Journal of Molecular Sciences*.

Andersen, O. M., & Markham, K. R. (2005). Flavonoids: Chemistry, Biochemistry and Applications. CRC Press. doi:10.1201/9781420039443

Aqil, F., & Ahmad, I. Z. M. T. U. (2006). Antioxidant and free radical scavenging properties of twelve traditionally used Indian medicinal plants. *Turkish Journal of Biology*, *30*(3), 177–183.

Arumugam, P., Priya, N. G., Subathra, M., & Ramesh, A. (2008). Anti-inflammatory activity of four solvent fractions of ethanol extract of *Mentha spicata* L. investigated on acute and chronic inflammation induced rats. *Environmental Toxicology and Pharmacology*, *26*(1), 92–95. doi:10.1016/j.etap.2008.02.008 PMID:21783894

Asada, K., & Takahashi, M. (1987). Production and scavenging of active oxygen in chloroplasts. In *Photoinhibition* (pp. 227–287). Photoinhibition.

Auddy, B., Ferreira, M., Blasina, F., Lafon, L., Arredondo, F., Dajas, F., & Mukherjee, B. (2003). Screening of antioxidant activity of three Indian medicinal plants, traditionally used for the management of neurodegenerative diseases. *Journal of Ethnopharmacology*, *84*(2-3), 131–138. doi:10.1016/S0378-8741(02)00322-7 PMID:12648805

Baba, S. A., Malik, A. H., Wani, Z. A., Mohiuddin, T., Shah, Z., Abbas, N., & Ashraf, N. (2015). Phytochemical analysis and antioxidant activity of different tissue types of *Crocus sativus* and oxidative stress alleviating potential of saffron extract in plants, bacteria, and yeast. *South African Journal of Botany*, *99*, 80–87. doi:10.1016/j.sajb.2015.03.194

Balasundram, N., Sundram, K., & Samman, S. (2006). Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food Chemistry*, *99*(1), 191–203. doi:10.1016/j.foodchem.2005.07.042

Barry, H. (1999). Food-derived antioxidants. Evaluating their importance in food and in vivo. *Food Science and Agricultural Chemistry*, *1*(2), 67–109.

Beltran, J. C. M., & Stange, C. (2016). Apocarotenoids: A new carotenoid-derived pathway. *Sub-Cellular Biochemistry*, *79*, 239–272. doi:10.1007/978-3-319-39126-7_9 PMID:27485225

Bhatt, I. D., Rawat, S., & Rawal, R. S. (2013). Antioxidants in medicinal plants. In *Biotechnology for Medicinal Plants* (pp. 295–326). Berlin: Springer Berlin Heidelberg. doi:10.1007/978-3-642-29974-2_13

Brewer, M. S. (2011). Natural Antioxidants: Sources, Compounds, Mechanisms of Action, and Potential Applications. *Comprehensive Reviews in Food Science and Food Safety*, *10*(4), 221–247. doi:10.1111/j.1541-4337.2011.00156.x

Cai, Y., Luo, Q., Sun, M., & Corke, H. (2004). Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. *Life Sciences*, *74*(17), 2157–2184. doi:10.1016/j.lfs.2003.09.047 PMID:14969719

Cai, Y. Z., Sun, M., Xing, J., Luo, Q., & Corke, H. (2006). Structure-radical scavenging activity relationships of phenolic compounds from traditional Chinese medicinal plants. *Life Sciences*, *78*(25), 2872–2888. doi:10.1016/j.lfs.2005.11.004 PMID:16325868

Cameron, E., & Pauling, L. (1976). Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proceedings of the National Academy of Sciences of the United States of America*, *73*(10), 3685–3689. doi:10.1073/pnas.73.10.3685 PMID:1068480

Chen, J. H., & Ho, C. T. (1997). Antioxidant Activities of Caffeic Acid and Its Related Hydroxycinnamic Acid Compounds. *Journal of Agricultural and Food Chemistry*, *45*(7), 2374–2378. doi:10.1021/jf970055t

Creagan, E. T., Moertel, C. G., O'Fallon, J. R., Schutt, A. J., O'Connell, M. J., Rubin, J., & Frytak, S. (1979). Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer: A controlled trial. *The New England Journal of Medicine*, *301*(13), 687–690. doi:10.1056/NEJM197909273011303 PMID:384241

Dastmalchi, K. D., Dorman, H. J., Koşar, M., & Hiltunen, R. (2007). Chemical composition and i*n vitro* antioxidant evaluation of a water-soluble moldavian balm (*Dracocephalum moldavica* L.) extract. *Lebensmittel-Wissenschaft + Technologie*, *40*(2), 239–248. doi:10.1016/j.lwt.2005.09.019

Deba, F., Xuan, T. D., Yasuda, M., & Tawata, S. (2013). Chemical composition and antioxidant, antibacterial and antifungal activities of the essential oils from *Bidens pilosa* Linn. var. Radiata. *Food Control*, *19*(4), 246–352.

Dulal, M. S. R., Taher, M. A., & Hossain, M. A. (2019). Antioxidant phytochemicals and some research on plants-A review. *World Journal of Pharmaceutical and Medical Research*, *5*(3), 40–45.

Fresco, P., Borges, F., Diniz, C., & Marques, M. P. M. (2006). New insights on the anticancer properties of dietary polyphenols. *Medicinal Research Reviews*, *26*(6), 747–766. doi:10.1002/med.20060 PMID:16710860

Gómez-García, M. D. R., & Ochoa-Alejo, N. (2013). Biochemistry and molecular biology of carotenoid biosynthesis in chili peppers (*Capsicum* spp.). *International Journal of Molecular Sciences*.

Gupta, S., Mediratta, P. K., Singh, S., Sharma, K. K., & Shukla, R. (2006). Antidiabetic, antihypercholesterolaemic and antioxidant effect of *Ocimum sanctum* (Linn) seed oil. *Indian Journal of Experimental Biology*, *44*(4), 300–304. PMID:16629372

Gupta, S., & Prakash, J. (2009). Studies on Indian green leafy vegetables for their antioxidant activity. *Plant Foods for Human Nutrition (Dordrecht, Netherlands)*, *64*(1), 39–45. doi:10.100711130-008-0096-6 PMID:18985454

Halliwell, B. (2007). Flavonoids: A re-run of the carotenoids story. *Novartis Foundation Symposium*, *282*, 93–104. doi:10.1002/9780470319444.ch7 PMID:17913226

Hollman, P. C., & Arts, I. C. (2000). Flavonols, flavones and flavanols - Nature, occurrence and dietary burden. *Journal of the Science of Food and Agriculture*.

Hollman, P. C. H., & Katan, M. B. (1999). Dietary flavonoids: Intake, health effects and bioavailability. *Food and Chemical Toxicology*, *37*(9-10), 937–942. doi:10.1016/S0278-6915(99)00079-4 PMID:10541448

Hou, X., Rivers, J., León, P., McQuinn, R. P., & Pogson, B. J. (2016). Synthesis and function of apocarotenoid Ssgnals in plants. *Trends in Plant Science*, *21*(9), 792–803. doi:10.1016/j.tplants.2016.06.001 PMID:27344539

Huang, W. Y., Cai, Y.-Z., Xing, J., Corke, H., & Sun, M. (2008). Comparative analysis of bioactivities of four *Polygonum* species. *Planta Medica*, *74*(1), 43–49. doi:10.1055-2007-993759 PMID:18067063

Huh, Y. S., Hong, T. H., & Hong, W. H. (2004). Effective extraction of oligomeric proanthocyanidin (OPC) from wild grape seeds. *Biotechnology and Bioprocess Engineering; BBE*, *9*(6), 471–475. doi:10.1007/BF02933488

Ighodaro, O. M., & Akinloye, O. A. (2018). First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria Journal of Medicine*, *54*(4), 287–293. doi:10.1016/j.ajme.2017.09.001

Imaida, K., Fukushima, S., Shirai, T., Ohtani, M., Nakanishi, K., & Ito, N. (1983). Promoting activities of butylated hydroxyanisole and butylated hydroxytoluene on 2-stage urinary bladder carcinogenesis and inhibition of γ-glutamyl transpeptidase-positive foci development in the liver of rats. *Carcinogenesis*, *4*(7), 895–899. doi:10.1093/carcin/4.7.895 PMID:6135514

Iriti, M., Faoro, F., Iriti, M., & Faoro, F. (2009). Chemical diversity and defence metabolism: How plants cope with pathogens and ozone pollution. *International Journal of Molecular Sciences*, *10*(8), 3371–3399. doi:10.3390/ijms10083371 PMID:20111684

Kopsell, D. A., & Kopsell, D. E. (2006). Accumulation and bioavailability of dietary carotenoids in vegetable crops. *Trends in Plant Science*, *11*(10), 499–507. doi:10.1016/j.tplants.2006.08.006 PMID:16949856

Kumari, A., & Kakkar, P. (2008). Screening of antioxidant potential of selected barks of indian medicinal plants by multiple in vitro assays. *Biomedical and Environmental Sciences*, *21*(1), 24–29. doi:10.1016/S0895-3988(08)60003-3 PMID:18478975

Kuo, Y. H., & Li, Y. C. (1997). Constituents of the bark of *Ficus microcarpa* L.f. *Journal of the Chinese Chemical Society (Taipei)*, *44*(3), 321–325. doi:10.1002/jccs.199700048

Lima, C. F., Valentao, P. C. R., Andrade, P. B., Seabra, R. M., Fernandes-Ferreira, M., & Pereira-Wilson, C. (2007). Water and methanolic extracts of Salvia officinalis protect HepG2 cells from t-BHP induced oxidative damage. *Chemico-Biological Interactions*, *167*(2), 107–115. doi:10.1016/j.cbi.2007.01.020 PMID:17349617

Maiga, A., Malterud, K. E., Diallo, D., & Paulsen, B. S. (2006). Antioxidant and 15-lipoxygenase inhibitory activities of the Malian medicinal plants *Diospyros abyssinica* (Hiern) F. White (Ebenaceae), *Lannea velutina* A. Rich (Anacardiaceae) and *Crossopteryx febrifuga* (Afzel) Benth. (Rubiaceae). *Journal of Ethnopharmacology*, *104*(1-2), 132–137. doi:10.1016/j.jep.2005.08.063 PMID:16213686

Merhan, O. (2017). The biochemistry and antioxidant properties of carotenoids. In *Carotenoids*. InTech. doi:10.5772/67592

Merken, H. M., & Beecher, G. R. (2000). Measurement of food flavonoids by high-performance liquid chromatography: A review. *Journal of Agricultural and Food Chemistry*, *48*(3), 577–599. doi:10.1021/jf990872o PMID:10725120

Miguel, M. G. (2010). Antioxidant activity of medicinal and aromatic plants. A review. *Flavour and Fragrance Journal*.

Mittler, R. (2017). ROS Are Good. *Trends in Plant Science*, *22*(1), 11–19. doi:10.1016/j.tplants.2016.08.002 PMID:27666517

Nishikimi, M., & Yagi, K. (2011). Biochemistry and molecular biology of ascorbic acid biosynthesis. In *Subcellular biochemistry* (pp. 17–39). Springer.

Öztürk, M., Aydoğmuş-Öztürk, F., Duru, M. E., & Topçu, G. (2007). Antioxidant activity of stem and root extracts of Rhubarb (*Rheum ribes*): An edible medicinal plant. *Food Chemistry*, *103*(2), 623–630. doi:10.1016/j.foodchem.2006.09.005

Padayatty, S. J., Katz, A., Wang, Y., Eck, P., Kwon, O., Lee, J. H., & Levine, M. (2003). Vitamin C as an antioxidant: Evaluation of its role in disease prevention. *Journal of the American College of Nutrition*, *22*(1), 18–35. doi:10.1080/07315724.2003.10719272 PMID:12569111

Pattanaik, B., & Lindberg, P. (2015). Terpenoids and their biosynthesis in cyanobacteria. *Life (Chicago, Ill.)*, *5*(1), 269–293. PMID:25615610

Pietta, P. G. (2000). Flavonoids as antioxidants. *Journal of Natural Products*, *63*(7), 1035–1042. doi:10.1021/np9904509 PMID:10924197

Pilarski, R., Zieliński, H., Ciesiołka, D., & Gulewicz, K. (2006). Antioxidant activity of ethanolic and aqueous extracts of *Uncaria tomentosa* (Willd.) DC. *Journal of Ethnopharmacology*, *104*(1-2), 18–23. doi:10.1016/j.jep.2005.08.046 PMID:16202551

Poltanov, E. A., Shikov, A. N., Dorman, H. J. D., Pozharitskaya, O. N., Makarov, V. G., Tikhonov, V. P., & Hiltunen, R. (2009). Chemical and antioxidant evaluation of Indian gooseberry (*Emblica officinalis* Gaertn., syn. *Phyllanthus emblica* L.) supplements. *Phytotherapy Research*, *23*(9), 1309–1315. doi:10.1002/ptr.2775 PMID:19172666

Pratt, D. E. (1992). *Natural antioxidants from plant material*. Academic Press.

Ramadan, G., Al-Kahtani, M. A., & El-Sayed, W. M. (2011). Anti-inflammatory and anti-oxidant properties of *Curcuma longa* (turmeric) versus *Zingiber officinale* (ginger) rhizomes in rat adjuvant-induced arthritis. *Inflammation*, *34*(4), 291–301. doi:10.100710753-010-9278-0 PMID:21120596

Ramalakshmi, K., Rahath Kubra, I., & Jagan Mohan Rao, L. (2008). Antioxidant potential of low-grade coffee beans. *Food Research International*, *41*(1), 96–103. doi:10.1016/j.foodres.2007.10.003

Randhir, R., Lin, Y. T., & Shetty, K. (2004). Phenolics, their antioxidant and antimicrobial activity in dark germinated fenugreek sprouts in response to peptide and phytochemical elicitors. *Asia Pacific Journal of Clinical Nutrition*, *13*(3), 295–307. PMID:15331344

Sabu, M. C., & Kuttan, R. (2009). Antidiabetic and antioxidant activity of *Terminalia belerica*. Roxb. *Indian Journal of Experimental Biology*, *47*(4), 270–275. PMID:19382723

Saha, K., Lajis, N. H., Israf, D. A., Hamzah, A. S., Khozirah, S., Khamis, S., & Syahida, A. (2004). Evaluation of antioxidant and nitric oxide inhibitory activities of selected Malaysian medicinal plants. *Journal of Ethnopharmacology*, *92*(2-3), 263–267. doi:10.1016/j.jep.2004.03.007 PMID:15138010

Saini, R. K., Nile, S. H., & Park, S. W. (2015). *Carotenoids from fruits and vegetables: Chemistry, analysis, occurrence, bioavailability and biological activities. In Food Research International*. Elsevier.

Schofield, P., Mbugua, D. M., & Pell, A. N. (2001). Analysis of condensed tannins: A review. In *Animal Feed Science and Technology*. Elsevier.

Shahidi, F. (2015). *Antioxidants: Principles and Applications. Handbook of Antioxidants for Food Preservation*. Elsevier Ltd.

Shahidi, F., Janitha, P. K., & Wanasundara, P. D. (1992). Phenolic antioxidants. *Critical Reviews in Food Science and Nutrition*, *32*(1), 67–103. doi:10.1080/10408399209527581 PMID:1290586

Sharififar, F., Dehghn-Nudeh, G., & Mirtajaldini, M. (2009). Major flavonoids with antioxidant activity from *Teucrium polium* L. *Food Chemistry*, *112*(4), 885–888. doi:10.1016/j.foodchem.2008.06.064

Singh, R., Singh, S., Kumar, S., & Arora, S. (2007). Evaluation of antioxidant potential of ethyl acetate extract/fractions of *Acacia auriculiformis* A. Cunn. *Food and Chemical Toxicology*, *45*(7), 1216–1223. doi:10.1016/j.fct.2007.01.002 PMID:17336438

Sokmen, M., Angelova, M., Krumova, E., Pashova, S., Ivancheva, S., Sokmen, A., & Serkedjieva, J. (2005). *In vitro* antioxidant activity of polyphenol extracts with antiviral properties from *Geranium sanguineum* L. *Life Sciences*, *76*(25), 2981–2993. doi:10.1016/j.lfs.2004.11.020 PMID:15820508

Surveswaran, S., Cai, Y. Z., Corke, H., & Sun, M. (2007). Systematic evaluation of natural phenolic antioxidants from 133 Indian medicinal plants. *Food Chemistry*, *102*(3), 938–953. doi:10.1016/j.foodchem.2006.06.033

Varma, N. (2016). Phytoconstituents and their mode of extractions: An overview. *Res. J. Chem. Environ. Sci*, *4*(2), 8–15.

Wagner, K. H., & Elmadfa, I. (2003). Biological relevance of terpenoids. *Annals of Nutrition & Metabolism*, *47*(3-4), 95–106. doi:10.1159/000070030 PMID:12743459

Waterman, P. G. (1993). Phytochemical dictionary: A handbook of bioactive compounds from plants. *Biochemical Systematics and Ecology*, *21*(8), 849. doi:10.1016/0305-1978(93)90098-C

Yabuzaki, J. (2017). *Carotenoids Database: Structures, chemical fingerprints and distribution among organisms. Database*. Oxford University Press.

Yabuzaki, J. (2018). *Carotenoid Database*. Retrieved June 19, 2019, from http://carotenoiddb.jp/

Chapter 14
Bryo-Pharmaceuticals: An Emerging Era of Pharmaceutical Products

Saumya Pandey
School of Agriculture, Uttaranchal University, India

Afroz Alam
Department of Bioscience and Biotechnology, Banasthali Vidyapith, India

ABSTRACT

Because bryophytes are a promising source of a large number of secondary metabolites, they are used efficiently in surgical dressing, herbal medicines, antibiotics, and other pharmaceutical products. The advent of several biotechnological tools and their utilization in the exploitation of pharmaceuticals properties of bryophytes leads to a new era of bryo-pharmaceuticals. Nowadays, the biopharmaceutical productions using moss system are gaining importance over other plant systems because of their unique properties such as predominant haploid gametophytic stage, stable gene integration, efficient secretary signals, and large-scale production in bioreactors. Several researchers have established moss system as safe and efficient for the production of several complex modified recombinant pharmaceuticals under standard conditions. The moss Physcomitrella patens are extensively exploited and commercialized as a production host for production of several recombinant proteins, human growth factors, antibiotics, and its derivatives.

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INTRODUCTION

Biopharmaceutical is defined as complex medicinal biomolecule which possesses pharmacological activity exploited for therapeutic or *in vivo* diagnostic purposes and are formed via genetic modification instead of extracting directly from indigenous biological sources (Ryu & Nam, 2000). They are large, complex macromolecules that are developed from living system. Biopharmaceuticals and synthetic drugs are different in all aspects such as source, composition, structure and properties of product, methods of development and handling; dosing and formulation; IPR (Intellectual Property Right), legal regulations and marketing strategy. Primarily, biopharmaceutical includes protein drugs such as monoclonal antibodies, attenuated vaccines and nucleic acid drugs that include DNA, RNA or antisense RNA oligonucleotides (Ryu *et al*., 2012). The production system widely used for development of these drugs includes plant cells, yeast, insect cells, bacteria and mammalian cells. The selection of production system for the development of drug usually depends on the specific properties of required protein. Biopharmaceuticals has significant position in the public health system of both developed and developing countries by combating several life-threatening diseases (Rencz *et al*., 2015).

With the advent of biotechnological tools such as RDT (recombinant DNA technology), the increased production of desired protein became possible by simply expressing the target cDNA in recombinant host organisms. In 1982, the Human insulin became first recombinant protein that was launched in the market and this further lead to the development of several other new biopharmaceuticals. Presently, over 300 proteins therapeutics have been permitted globally by the FDA (Food and Drug Administration, US) for humans use and several drugs are under clinical trials (Lawrence, 2007). In 2004, the market size estimation for recombinant therapeutics was nearly 44 billion and these values will be even higher in the future (Lawrence, 2005). Thus, the biopharmaceutical industries are most rapidly growing sector of industrial biotechnology.

Microbial or mammalian systems (Chinese Hamster Ovary cells) have been extensively exploited production organisms for the vast variety of therapeutic protein (Schmidt, 2004). The major advantage of using microbial system is easy handling, well understood growth characteristics high product yield and relatively low cost. Most exploited microbial system for production of biopharmaceuticals is *E.coli* which is extensively used production system for small recombinant proteins. The major limitation of microbial system is lack of posttranslational modification of target protein and presence of bacterial lippopolysaccharids. However the mammalian cell lines (e.g., Chinese haster ovary cells, rodent cell lines and human cell lines) can provide correct posttranslational modification of the target proteins and used for production of recombinant protein. The major drawback of this system

is contamination of cell lines with animal viruses. (Butler, 2005; Walsh & Jefferis, 2006). However, as the need for protein therapeutics is increasing day by day the quest for probable production system is also escalating. In addition, the production organisms with the efficient posttranslational modification of proteins have aroused as matter of concern for the researcher. The benefits offered by plant derived system are far greater than conventional production systems and thus used extensively as production systems for the therapeutic protein.

Plant when used as production system offers the following benefits: (1) low production cost, (2) synthesis of complex multimeric proteins and relatively similar posttranslational modification machinery as mammals, (3) the chance of contamination by human disease causing agent is low (Fischer *et al*., 2004), (4) the production of plants can be done in accordance of GMP (Good Manufacturing Practices) guidelines by growing the plants in controlled and standardized conditions via *in vitro* plant tissue culture (Ma *et al*., 2003), (5) easier and well-studied transformation methods (Schillberg *et al*., 2004), (6) edible plants with oral immunogenic recombinant proteins can be developed which is administered orally and thus the protein purification step is not needed. These advantages make it preferred choice as an expression host for production of several pharmaceutical proteins from more than 15 years.

In 2012, the first FDA approved plant-derived biopharmaceuticals; the recombinant human glucocerebrosidase is produced in the plant cell lines and launched in the market with brand name Elelyso. This drug is employed for curing Gaucher's disease. The treatment cost/patient/year is reduced from US$200,000 (Orphan drug) to US$1500, 000 by the use of this drug (Kesik-Brodacka, 2017).

To date, seed plants such as tobacco, corn, alfalfa have been extensively used for molecular farming. Although bryophytes shown similarity in evolutionary history to higher plants and also depict ethno-medicinal value, the thorough investigation of bryophytes for new therapeutic compounds were ignored because of their miniature size and difficulty in identification. Earlier reports on secondary metabolites of this neglected group have suggested the occurrence of some novel metabolites which are absent in higher plants. These days' researchers have focused their attention on the unexplored group of plants, bryophytes as an innovative tool for molecular farming. *P. patens* is widely exploited and commercialized as substitute for the production of biopharmaceuticals owing to its cheap, large-scale *in vitro* culture in photo-bioreactors and unparalleled property of specific genetic modifications (Decker & Reski, 2008).

The present chapter mainly compiles the information about the therapeutic potential of bryophytes together with the biotechnological tools which make bryophytes as an efficient production system for the development of biopharmaceutical drugs. This chapter also provides information about the biopharmaceutical products produced using moss as a production system and their pharmacological applications.

POTENTIAL OF BRYOPHYTES AS THERAPEUTICS

As the mosses are a promising source of a large number of secondary metabolites, they are used efficiently in surgical dressings, herbal medicines, antibiotics and other pharmaceutical products. The studies based on phytochemistry of bryophytes suggests the presence of variety of pharmacologically active compounds for example carbohydrates, lipids, proteins, fatty acids, steroids, organic acids, polyphenols, sugar alcohol, aliphatic and aromatic compounds, acetogenins and phenyl-quinines in bryophytes responsible for its several bioactivities (Asakawa, 2007; Alam, 2012). These plants are used worldwide by different tribal communities for curing various diseases in day to day life (Chandra *et al*., 2017). The number of the naturally derived components have shown several biological activities such as antimicrobial, antitumor, antifungal, vasopressin antagonist, cytotoxic, cardiotonic, allergic causing, insecticidal and piscicidal, thus useful in the pharamaceutical industry (Sabovljevic *et al.,* 2011).

Several species of bryophytes have been used widely as medicines in homeopathy. The polyphenolic compounds isolated from several species of bryophytes have shown antimicrobial activities for example genus *Sphagnum, Mnium, Atrichum*, *Polytrichum*, *Dicranum* and *Mnium* Beside antibacterial properties some bryophytes have also shown efficient antifungal properties against several human disease causing fungus. In rare cases the bioactive compounds isolated from bryophytes may also cause dermatitis and allergic reactions. In addition, various bioactive compounds isolated from bryophytes showed anti-cancerous efficacy on several cancer cell lines such as MCF7 (breast cancer cell), P-388 (murine leukemia tumor), LOVO (colon adenocarcinoma cell), A549 (lung carcinoma), A172 (glioma cells), HEP-G2 (liver hepatoblastoma), U87 (glioma cells), MDA-MB-435 (breast ductal carcinoma) (MDA-MB-435) etc., (Dey & Mukherjee, 2015). Several bryophyte species such as *Riccia, Marchantia, Barbula, Fontinalis* and *Bryum* have been efficiently used for the treatment of wide range of diseases like skin diseases, fever, wound healing, lung and cardiovascular diseases, inflammation, and infections (Glime, 2007). Although only small number of mosses (3.2%) and liverworts (8.8%) taxa have been thoroughly examined for the pharmacologically active compound but their mechanisms of action are yet to be explored (Mishra *et al*., 2014). The list of a few bioactive compounds isolated from some bryophytes and their medicinal uses are given in table 1.

MOSS AS AN EMERGING SOURCE OF BRYO-PHARMACEUTICAL: SIGNIFICANCE AND BENEFITS

Bryophytes have been exploited extensively to understand the genetic basis of the evolutionary and developmental biology of land plants (Pandey & Alam, 2016). Presently it is also emerging as a suitable host for production of several biopharmaceutical products. Beside used as model plants, moss *P. patens* have been used widely as innovative tools as the host for bryopharmaceutical products. The advents of several advance biotechnological tools and the benefits associated with the use of this ignored group have gained focus of researchers as potential biopharmaceutical production host. The moss-system as production host for bryopharmaceutical production offer following benefits:

Efficient in Vitro Cultivation

Small-scale cultivation is done in glass flask agitated on simple shaker while large-scale cultivation is performed in photo-bioreactors which provide highly controlled and stabilized conditions for the growth of moss. The *in vitro* cultivation not only provides mass production and fulfills the safety guidelines but also allows easy and cost-effective downstream processing of the biopharmaceuticals (Reski *et al*., 2015). For multigene targeting in single experiment the protocol for isolation and regeneration of protoplast and PEG-mediated transformation has been standardized by several researchers.

Efficient Homologous Recombination

Mosses show more effective homologous recombination than other multicellular plants. Homologous recombination-mediated gene targeting allows knockout of genes thus act as a potent tool for designing of effective production host variety (Pandey & Alam, 2016). However, the alternative approaches such as use of artificial micro-RNA that cause down-regulation of gene expression rather than complete destruction of gene as in gene targeting, has also been recognized in *P. patens.*

Dominant Gametophytic Phase

The dominant gametophytic (haploid) generation in the life cycle of mosses is advantageous for genetic study.

Table 1. List of some bioactive compounds isolated from various medicinal bryophytes

Isolated Bioactive compounds	Bryophyte species	Medicinal Uses	References
	MOSSES		
p-Hydroxycinnamic Acid, 7-8-Dihydroxycoumarin	*Rhodobryum giganteum* (Schwaegr.)Par.	To treat cardiovascular disease and nervous prostration. anti-hypoxia, antipyretic, diuretic and antihypertensive	Asakawa, (2007)
Pallidisetin A Pallidisetin B	*Polytrichum pallidisetum*	Anticancer properties	Zheng *et al*., (1994)
Communin A Communin B	*Polytrichum commune*	Anticancer properties	Fu *et al*., (2009)
Triterpenoidal saponins	*Philonotis* sp. *Plagiomnium* sp. *Mnium* sp.	Heal burns, adeno-pharyngitis, antipyretic, antidotal and antibiotics Against swelling and to set broken bones	Azuelo *et al*., (2011)
Fulvic acid	*Sphagnum* peat	Cytotoxic effect	Yamada *et al*., (2007)
	Liverwort		
Asterelin A, Asterelin B,	*Asterella agusta*	Antifungal properties against human pathogen *Candida albicans*	Qu *et al*., (2007)
Riccardins A Riccardins B l	*Riccardia multifida*	Exhibits anti-leukemic activity	Azuelo *et al*., (2011)
Riccardin H Riccardin D,	*Dumortiera hirsute*	Antifungal properties against human pathogen *C. albicans,* antiproliferative effect on human leukemia cell lines.	Cheng *et al*., (2001)
Diplophylline	*Diplophyllum albicans D. taxifolium*	Anticancer property against human epidermiod carcinoma	Saxena, (2004)
Marchantin A Marchantin C Marchantin D	*Marcantia polymorpha, M. palmate Dumortiera hirsute*	Treat diuretics, liver ailments, pulmonary tuberculosis, cardiovascular disease boils and abscess. Antifungal activity against human pathogen *C. albicans*	Niu *et al*., (2006)
Isoplagiochins A Isoplagiochins B	*Plagiochila fruticosa*	inhibitory effect on tubulin polymerization	Morita *et al*., (2009)
Perrottetin E	*Radula perrottetii*	Cytotoxicity against the KB cells	Asakawa *et al*., (1982)
Dihydroptychantol A	*Asterella angusta*	Reversal effect on multidrug resistance	Li *et al*., (2009)
Lunularin	*Dumortiera hirsuta*	Cytotoxicity against human HepG2 cells	Lu *et al*., (2006)
Bicyclohumulenone, Plagiochiline-A, Plagiochilide, Plagiochilal B	*Pallavicinia* sp.	Exhibits antileukemic/anti-microbial activity	Azuelo *et al*., (2011)
Menthanemono terpenoids Sacullatal	*Plagiochila* sp.	Antimicrobial activity	Azuelo *et al*., (2011)
Pakyonol	*Plagiochasma intermedium*	effective against chemoresistant prostate cancer PC3 cells	Xu *et al*., (2010)
Costunolide Tulipinolide	*Conocephalum supradecompositum Frullania monocera*, *Frullania tamarisci*, *Marchantia polymorpha*, *Porella japonica*	Antitumor and anticancer potential	Asakawa, (1981)
Naviculyl caffeate	*Bazzania novae-zelandiae*	Active against human tumour cell lines	Burgess *et al*., (2000)

Easy Manipulation of Glycosylation Pathway

The manipulation of the glycosylation pathway is possible in mosses in contrast to seed plants. The plant N-glycans attached with xylose and fucose residue are associated with allergic risk thus it should be removed for the production of biopharmaceuticals (Reski *et al*., 2015).

Extensive Posttranslational Processing

As mosses are higher multicellular eukaryotes they show extensive posttranslational protein modification such as the formation of disulfide bridges and complex glycosylation. The glycosylation may possibly be essential for the stability, activity or immunogenicity of the products (Walsh & Jefferis, 2006).

Secondary Metabolism

The genes associated with secondary metabolism are relatively greater in mosses as compared to higher plants (Rensing *et al*., 2007). Among these, the health benefits of some genes are well studied while far more are yet to discover.

MOLECULAR CHARACTERIZATION AND THERAPEUTIC APPLICATIONS OF BRYO-PHARMACEUTICALS PRODUCED IN MOSS SYSTEM

The plant based production host has been extensively used for the production of several pharmaceutical products such as mAbs (monoclonal antibodies), human growth hormone, interferon, fusion protein, serum albumin, etc. Among plant system, mosses are emerging as a potential source of biopharmaceuticals. Several therapeutic proteins produced in moss system are discussed below.

Vaccines

The development of low-cost edible vaccine is a major concern among researcher. The moss system offers several unique advantages such as low production cost, increased safety, stability, versatility, and efficacy. In addition, the consumption of moss as shown no adverse effects and thus the vaccine-producing moss can be used directly as an oral vaccine. These properties make the moss system as prospective host for the production of vaccines (Rosales-Mendoza *et al*., 2014). Poly-HIV is the

first vaccine developed in the moss system which is a chimeric Env-derived HIV multi-epitope protein (Orellana-Escobedo *et al*., 2015).

Antibodies

Monoclonal antibodies (mAbs) are used extensively for both therapeutic and diagnostic purposes. Nearly dozen of FDA-approved mAbs are available in the market, and about 700 therapeutics antibodies may be under development (Humphreys & Glover, 2001). Plant system emerges as a potential host for the production of large quantities of mAbs and so referred as "plantbodies". The moss was used as the efficient system for the production of glyco-optimized mAbs (IgG1 IGN314) to facilitate the recognition of a tumor associated glycosylation patterns. This antibody has shown 40 times more efficacy in destroying tumor cell lines as compared to same antibody produced using CHO system as host (Schuster *et al*., 2007). In contrast to mammals, the sugar moiety (α-1, 6-linked fucose residue) at the base of the bi-antennary N-glycan structure is absent in plants. Thus, the antibody-dependent cellular cytotoxicity (ADCC) of antibody derived from moss system was apparently higher than that produced in CHO cells (Kircheis *et al*., 2012).

Hormones

Erythropoietin (EPO), a chief hematopoietic hormone (cytokine) causes maturation of erythrocytes in bone marrow. Besides this, it also has an important role in apoptosis prevention, neurogenesis, immune response, kidney function and angiogenesis (Lombardero *et al*., 2011). The moss system has been utilized for the production of functional EPO (Weise *et al*., 2007). On the other hand, the protein produced using such host contains Lewis-A (Lea) structure which are biomarkers for some form of cancer and thus imposes a limitation in use as plant-made pharmaceuticals (Rho *et al*., 2014). Consequently, the gene accountable for the formation of Lea epitopes has been identified and removed from the genome of moss *P. patens*. Such Erythropoietin which is devoid of Lea epitopes and any other plant-typical glyco-epitopes has been produced in moss system known as asialo-EPO (AEPO) (Parsons *et al*., 2012). The asialo-EPO shows the neuroprotective and anti-apoptotic effect and thus useful in stroke treatment lacking the thromboembolic risk associated with the EPO (Kaneko *et al*., 2013). EPO is also used in illegal doping activities whereas asialo-EPO which is devoid of capability to cause maturation of erythrocytes cannot be used in such illegal activities.

Further, the safety and efficacy of moss-derived asialo-EPO were enhanced by identifying and deleting the gene that causes an unwanted non-human prolyl-hydroxylation from the moss genome.

Enzymes

The moss system has been used as a host for the production of enzymes α-galactosidase (α-Gal) and β- glucocerebrosidase that are employed for the treatment of Fabry and Gaucher disease respectively. Usually the enzyme replacement therapy is used for the treatment of two orphan lysosomal storage diseases i.e. Morbus Gaucher and Morbus Fabry disease (Beck, 2010). The homogeneity and batch to batch stability of moss derived drugs are higher than that produced in mammalian cell lines (Niederkruger *et al*., 2014). The α-Gal produced in moss system has been reported to have better pharmacokinetics in Fabry mice as it lacks the terminal mannose phosphorylation and thus it uses mannose-6 phosphate receptors instead of mannose receptors for delivery in cells. Currently, Moss-made aGal is under clinical trials.

Moss system have also been used for the production of several reporter proteins such as bacterial beta-glucuronidase (GUS) (Reutter & Reski, 1996) and alpha-amylase (AMY), GFP-talin (Saidi *et al*., 2005) and human placental derived alkaline phosphatase (SEAP) (Gitzinger *et al*., 2009).

OTHER RECOMBINANT PRODUCTS

Several human growth factors for example Epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), Hepatocyte growth factor (HGF) and Keratinocyte growth factor (FGF7/KGF) has been produced by using moss as production host (Niederkruger *et al*., 2014). Although, vascular endothelial growth factor (VEGF) turn out to be the first human protein that was produced using moss system (Baur *et al*., 2005) which plays important role in angiogenesis and cancer (Goel and Mercurio, 2013). But first commercialized human protein that was produced using moss system was keratinocyte growth factor FGF7/KGF.

In addition, the moss system has also been successfully utilized for the production of full-length human complement factor (FH) which is needed for the treatment of age-related muscular degeneration (AMD) as well as diseases related to kidney (eg., atypical hemolytic uremic syndrome, C3 glomerulopathies) (Bradley *et al*., 2011; Sethi *et al*., 2012). The moss-derived FH is cheap and has no severe side effects and thus can be used as a substitute to the monoclonal antibody eculizumab (Schmidtko *et al*., 2013). The metabolic engineering of moss species has also enabled the enhanced production of commercially important bioactive compounds. For example, enzyme taxadiene synthase which acts as a precursor for the synthesis of anticancer drug paclitaxel is expressed in moss for enhanced production (Baird *et al*., 2010). Human serum albumin (HAS) that provides stability to secreted biopharmaceuticals is also expressed in moss system (Baur *et al*., 2005).

FUTURE PROSPECTS

Due to unique characteristic property exhibited by the moss system as production host their use for development of therapeutic protein, antibodies and vaccines, antibodies with novel pharmacological activity is gaining popularity among researchers. With the advent of innovative technologies, the significant economic values of these ignored groups of plants can be explored more precisely. The availability of genome sequence information and transformation techniques are limited to only a few species. In addition, more efforts are needed to develop new methods to increase yield, large scale production, distribution and handling of transgenic plant material and for efficient recovery of pharmaceutical products from the moss system. Also the commercialization of bryo-pharmaceuticals requires scaling-up of process under GMP certified conditions.

CONCLUSION

Currently, mammalian and microbial cells are exploited immensely as production host for wide varieties of biopharmaceuticals. Also to fulfill the increasing demand of recombinant biopharmaceuticals, the plant-based system is gaining popularity as production host for a variety of therapeutic protein. Also the development of new biotechnological tools facilitates the cost-effective analysis of novel bioactive compound, production and downstream processing of recombinant therapeutic proteins. Nowadays, among plant-based systems, the moss systems are gaining the attention of researchers because of its unique properties. Several bryo-pharmaceuticals has been developed using the moss-made system and are under clinical and preclinical trials. The bryo-pharmaceuticals are reported to have superior quality as compared to conventional products developed from a mammalian cell.

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REFERENCES

Alam, A. (2012). Some Indian bryophytes known for their biologically active compounds. *International Journal of Applied Biology and Pharmaceutical Technology*, *3*(2), 239–246.

Asakawa, Y. (1981). Biologically active substances obtained from bryophytes. *The Journal of the Hattori Botanical Laboratory*, (50): 123–142.

Asakawa, Y. (2007). Biologically active compounds from bryophytes. *Pure and Applied Chemistry*, *79*(4), 557–580. doi:10.1351/pac200779040557

Asakawa, Y., Toyota, M., Taira, Z., & Takemoto, T. (1982). Biologically active cyclic bisbenzyls and terpenoids isolated from liverworts. *Proceeding of the 25th Symposium on Chemistry of Natural Products*, 337-344.

Azuelo, A. G., Sariana, L. G., & Pabulan, M. P. (2011). Some medicinal bryophytes: Their Ethnomedical Uses and Morphology. *Asian Journal of Biodiversity*, *2*(1), 49–80. doi:10.7828/ajob.v2i1.92

Baird, R. D., Tan, D. S. P., & Kaye, S. B. (2010). Weekly paclitaxel in the treatment of recurrent ovarian cancer. *Clinical Oncology*, *7*(10), 575–582. PMID:20683437

Baur, A., Reski, R., & Gorr, G. (2005). Enhanced recovery of a secreted recombinant human growth factor using stabilizing additives and by coexpression of human serum albumin in the moss *Physcomitrella patens. Plant Biotechnology Journal*, *3*(3), 331–340. doi:10.1111/j.1467-7652.2005.00127.x PMID:17129315

Beck, M. (2010). Emerging drugs for lysosomal storage diseases. *Expert Opinion on Emerging Drugs*, *15*(3), 495–507. doi:10.1517/14728214.2010.498580 PMID:20557271

Bradley, D. T., Zipfel, P. F., & Hughes, A. E. (2011). Complement in age-related macular degeneration: A focus on function. *Eye (London, England)*, *25*(6), 683–693. doi:10.1038/eye.2011.37 PMID:21394116

Burgess, E. J., Larsen, L., & Perry, N. B. (2000). A Cytotoxic sesquiterpene caffeate from the Liverwort Bazzania n ovae-zelandiae. *Journal of Natural Products*, *63*(4), 537–539. doi:10.1021/np990492x PMID:10785435

Butler, M. (2005). Animal cell cultures: Recent achievements and perspectives in the production of biopharmaceuticals. *Applied Microbiology and Biotechnology*, *68*(3), 283–291. doi:10.100700253-005-1980-8 PMID:15834715

Chandra, S., Chandra, D., Barh, A., Pankaj, Pandey, R. K., & Sharma, I. P. (2017). Bryophytes: Hoard of remedies, an ethno-medicinal review. *Journal of Traditional and Complementary Medicine*, *7*(1), 94–98. doi:10.1016/j.jtcme.2016.01.007 PMID:28053893

Cheng, A., Sun, L., Wu, X., & Lou, H. (2001). The inhibitory effect of a monocyclic bisbibenzylricardin D on the biofilms of *Candida albicans. Biological & Pharmaceutical Bulletin*, *32*(8), 1417–1421. doi:10.1248/bpb.32.1417 PMID:19652383

Decker, E. L., & Reski, R. (2008). Current achievements in the production of complex biopharmaceuticals with moss bioreactors. *Bioprocess and Biosystems Engineering*, *31*(1), 3–9. doi:10.100700449-007-0151-y PMID:17701058

Dey, A., & Mukherje, A. (2015). Therapeutic potential of bryophytes and derived compounds against cancer. *Journal of Acute Disease*, *4*(3), 236–248. doi:10.1016/j.joad.2015.04.011

Fischer, R., Stoger, E., Schillberg, S., Christou, P., & Twyman, R. M. (2004). Plant-based production of biopharmaceuticals. *Current Opinion in Plant Biology*, *7*(2), 152–158. doi:10.1016/j.pbi.2004.01.007 PMID:15003215

Fu, P., Lin, S., Shan, L., Lu, M., Shen, Y. H., Tang, J., ... Zhang, W. D. (2009). Constituents of the moss *Polytrichum commune. Journal of Natural Products*, *72*(7), 1335–1337. doi:10.1021/np800830v PMID:19572610

Gitzinger, M., Parsons, J., Reski, R., & Fussenegger, M. (2009). Functional cross-kingdom conservation of mammalian and moss (*Physcomitrella patens*) transcription, translation and secretion machineries. *Plant Biotechnology Journal*, *7*(1), 73–86. doi:10.1111/j.1467-7652.2008.00376.x PMID:19021876

Glime, J. M. (2007). Economic and ethnic uses of bryophytes. *Flora of North America*, *27*, 14–41.

Goel, H. L., & Mercurio, A. M. (2013). VEGF targets the tumor cell. *Nature Reviews. Cancer*, *13*(12), 871–882. doi:10.1038/nrc3627 PMID:24263190

Humphreys, D. P., & Glover, D. J. (2001). Therapeutic antibody production technologies: Molecules, applications, expression, and purification. *Current Opinion in Drug Discovery & Development*, *4*(2), 172–185. PMID:11378956

Kesik-Brodacka, M. (2017). Progress in biopharmaceutical development. *Biotechnology and Applied Biochemistry*, *65*(3), 306–322. doi:10.1002/bab.1617 PMID:28972297

Kircheis, R., Halanek, N., Koller, I., Jost, W., Schuster, M., Gorr, G., ... Nechansky, A. (2012). Correlation of ADCC activity with cytokine release induced by the stably expressed, glyco-engineered humanized Lewis Y specific monoclonal antibody MB314. *mAbs*, *4*(4), 532–541. doi:10.4161/mabs.20577 PMID:22665069

Lawrence, S. (2005). Biotech drug market steadily expands. *Nature Biotechnology*, *23*(12), 14–66. doi:10.1038/nbt1205-1466 PMID:16333279

Lawrence, S. (2007). Pipelines turn to biotech. *Nature Biotechnology*, *25*(12), 13–42. doi:10.1038/nbt1207-1342 PMID:18066015

Li, X., Sun, B., Zhu, C. J., Yuan, H. Q., Shi, Y. Q., Gao, J., ... Lou, H. X. (2009). Reversal of p-glycoprotein-mediated multidrug resistance by macrocyclic bisbibenzyl derivatives in adriamycin-resistant human myelogenous leukemia (K562/A02) cells. *Toxicology In Vitro*, *23*(1), 29–36. doi:10.1016/j.tiv.2008.09.015 PMID:18938236

Lombardero, M., Kovacs, K., & Scheithauer, B. W. (2011). Erythropoietin: A hormone with multiple functions. *Pathobiology*, *78*(1), 41–53. doi:10.1159/000322975 PMID:21474975

Lou, H. X., Li, G. Y., & Wang, F. Q. (2002). A cytotoxic diterpenoid and antifungal phenolic compounds from *Frullania muscicola* Steph. *Journal of Asian Natural Products Research*, *4*(2), 87–94. doi:10.1080/10286020290027353 PMID:12067164

Lu, Z. Q., Fan, P. H., Ji, M., & Lou, H. X. (2006). Terpenoids and bisbibenzyls from Chinese liverworts *Conocephalum conicum* and *Dumortiera hirsuta*. *Journal of Asian Natural Products Research*, *8*(1-2), 187–192. doi:10.1080/1028602042000325537 PMID:16753803

Ma, J. K., Drake, P. M., & Christou, P. (2003). Genetic modification: The production of recombinant pharmaceutical proteins in plants. *Nature Reviews. Genetics*, *4*(10), 794–805. doi:10.1038/nrg1177 PMID:14526375

Mishra, R., Pandey, V. K., & Chandra, R. (2014). Potential of Bryophytes as therapeutics. *International Journal of Pharmaceutical Sciences and Research*, *5*(9), 3584–3593.

Morita, H., Tomizawa, Y., Tsuchiya, T., Hirasawa, Y., Hashimoto, T., & Asakawa, Y. (2009). Antimitotic activity of two macrocyclic bis (bibenzyls), isoplagiochins A and B from the liverwort Plagiochila fruticosa. *Bioorganic & Medicinal Chemistry Letters*, *19*(2), 493–496. doi:10.1016/j.bmcl.2008.11.036 PMID:19056262

Niederkruger, H., Dabrowska-Schlepp, P., & Schaaf, A. (2014). Suspension culture of plant cells under phototrophic conditions. In H.P. Meyer & D.R. Schmidhalter (Ed.), Industrial Scale Suspension Culture of Living Cells. Weinheim: Wiley-VCH Verlag GmbH & Co. KGa-A. doi:10.1002/9783527683321.ch08

Niu, C., Qu, J. B., & Lou, H. X. (2006). Antifungal bis [bibenzyls] from the Chinese liverwort *Marchantia polymorpha* L. *Chemistry & Biodiversity*, *3*(1), 34–40. doi:10.1002/cbdv.200690004 PMID:17193213

Orellana-Escobedo, L., Rosales-Mendoza, S., Romero-Maldonado, A., Parsons, J., Decker, E. L., Monreal-Escalante, E., ... Reski, R. (2015). An Env-derived multi-epitope HIV chimeric protein produced in the moss *Physcomitrella patens* is immunogenic in mice. *Plant Cell Reports*, *34*(3), 425–433. doi:10.100700299-014-1720-6 PMID:25477207

Pandey, S., & Alam, A. (2016). *Marchantia polymorpha* L.: An emerging model plant system to study contemporary plant biology – A Review. *Plant Science Today*, *3*(2), 88–99. doi:10.14719/pst.2016.3.2.221

Parsons, J., Altmann, F., Arrenberg, C. K., Koprivova, A., Beike, A. K., Stemmer, C., ... Decker, E. L. (2012). Moss-based production of asialo-erythropoietin devoid of Lewis A and other plant-typical carbohydrate determinants. *Plant Biotechnology Journal*, *10*(7), 851–861. doi:10.1111/j.1467-7652.2012.00704.x PMID:22621344

Qu, J., Xie, C., Guo, H., Yu, W., & Lou, H. (2007). Antifungal dibenzofuran bis (bibenzyl) from the liverwort *Asterella angusta*. *Phytochemistry*, *68*(13), 1767–1774. doi:10.1016/j.phytochem.2007.04.036 PMID:17570447

Rencz, F., Péntek, M., Bortlik, M., Zagorowicz, E., Hlavaty, T., Śliwczyński, A., ... Lakatos, P. L. (2015). Biological therapy in inflammatory bowel diseases: Access in Central and Eastern Europe. *World Journal of Gastroenterology: WJG*, *21*(6), 17–28. doi:10.3748/wjg.v21.i6.1728 PMID:25684937

Rensing, S. A., Ick, J., Fawcett, J. A., Lang, D., Zimmer, A., Van de Peer, Y., & Reski, R. (2007). An ancient genome duplication contributed to the abundance of metabolic genes in the moss *Physcomitrella patens*. *BMC Evolutionary Biology*, *7*(1), 130. doi:10.1186/1471-2148-7-130 PMID:17683536

Reski, R., Parsons, J., & Decker, E. L. (2015). Moss-made pharmaceuticals: From bench to bedside. *Plant Biotechnology Journal*, *13*(8), 1191–1198. doi:10.1111/pbi.12401 PMID:26011014

Reutter, K., & Reski, R. (1996). Production of a heterologous protein in bioreactor cultures of fully differentiated moss plants. *Plant Tissue Culture & Biotechnology*, *2*, 142–147.

Rho, J., Mead, J. R., Wright, W. S., Brenner, D. E., Stave, J. W., Gildersleeve, J. C., & Lampe, P. D. (2014). Discovery of sialyl Lewis A and Lewis X modified protein cancer biomarkers using high density antibody arrays. *Journal of Proteomics*, *96*, 291–299. doi:10.1016/j.jprot.2013.10.030 PMID:24185138

Rosales-Mendoza, S., Orellana-Escobedo, L., Romero-Maldonado, A., Decker, E. L., & Reski, R. (2014). The potential of *Physcomitrella patens* as a platform for the production of plant-based vaccines. Expert Rev. *Expert Review of Vaccines*, *13*(2), 203–212. doi:10.1586/14760584.2014.872987 PMID:24405402

Ryu, D. D. Y., & Nam, D. H. (2000). Recent progress in biomolecular engineering. *Biotechnology Progress*, *16*(1), 2–16. doi:10.1021/bp088059d PMID:10662483

Ryu, J. K., Kim, H. S., & Nam, D. H. (2012). Current status and perspectives of biopharmaceutical drugs. *Biotechnology and Bioprocess Engineering; BBE*, *17*(5), 900–911. doi:10.100712257-012-0095-1

Sabovljević, A., Soković, M., Glamočlija, J., Ćirić, A., Vujičić, M., Pejin, B., & Sabovljević, M. (2011). Bio-activities of extracts from some axenically farmed and naturally grown bryophytes. *Journal of Medicinal Plants Research*, *5*(4), 565–571.

Saidi, Y., Finka, A., Chakhporanian, M., Zryd, J.-P., Schaefer, D. G., & Goloubinoff, P. (2005). Controlled expression of recombinant proteins in *Physcomitrella patens* by a conditional heat-shock promoter: A tool for plant research and biotechnology. *Plant Molecular Biology*, *59*(5), 697–711. doi:10.100711103-005-0889-z PMID:16270224

Saxena, D., & Harinder. (2004). Uses of bryophytes. *Resonance*, *9*(6), 56–65. doi:10.1007/BF02839221

Schillberg, S., Twyman, R. M., & Fischer, R. (2005). Opportunities for recombinant antigen and antibody expression in transgenicn plants-technology assessment. *Vaccine*, *23*(15), 1764–1769. doi:10.1016/j.vaccine.2004.11.002 PMID:15734038

Schmidt, F. R. (2004). Recombinant expression systems in the pharmaceutical industry. *Applied Microbiology and Biotechnology*, *65*(4), 363–372. doi:10.100700253-004-1656-9 PMID:15480623

Schmidtko, J., Peine, S., El-Housseini, Y., Pascual, M., & Meier, P. (2013). Treatment of atypical hemolytic uremic syndrome and thrombotic microangiopathies: A focus on Eculizumab. *American Journal of Kidney Diseases*, *61*(12), 289–299. doi:10.1053/j.ajkd.2012.07.028 PMID:23141475

Schuster, M., Jost, W., Mudde, G. C., Wiederkum, S., Schwager, C., Janzek, E., ... Gorr, G. (2007). *In vivo* glycoengineered antibody with improved lytic potential produced by an innovative non-mammalian expression system. *Biotechnology Journal: Healthcare Nutrition Technology*, *2*(6), 700–708. doi:10.1002/biot.200600255 PMID:17427997

Sethi, S., Nester, C. M., & Smith, R. J. H. (2012). Membranoproliferative glomerulonephritis and C3 glomerulopathy: Resolving the confusion. *Kidney International*, *81*(5), 434–441. doi:10.1038/ki.2011.399 PMID:22157657

Walsh, G., & Jefferis, R. (2006). Post-translational modifications in the context of therapeutic proteins. *Nature Biotechnology*, *24*(10), 1241–1252. doi:10.1038/nbt1252 PMID:17033665

Weise, A., Altmann, F., Rodriguez-Franco, M., Sjoberg, E. R., Baumer, W., Launhardt, H., ... Gorr, G. (2007). High-level expression of secreted complex glycosylated recombinant human erythropoietin in the Physcomitrella D-fuc-t D-xyl-t mutant. *Plant Biotechnology Journal*, *5*(3), 389–401. doi:10.1111/j.1467-7652.2007.00248.x PMID:17359496

Xu, A. H., Hu, Z. M., Qu, J. B., Liu, S. M., Syed, A. K. A., Yuan, H. Q., & Lou, H. X. (2010). Cyclic bisbibenzyls induce growth arrest and apoptosis of human prostate cancer PC3 cells. *Acta Pharmacologica Sinica*, *31*(5), 609–615. doi:10.1038/aps.2010.37 PMID:20418896

Yamada, P., Isoda, H., Han, J. K., Talorete, T. P., Yamaguchi, T., & Abe, Y. (2007). Inhibitory effect of fulvic acid extracted from Canadian sphagnum peat on chemical mediator release by RBL-2H3 and KU812 cells. *Bioscience, Biotechnology, and Biochemistry*, *71*(5), 1294–1305. doi:10.1271/bbb.60702 PMID:17485833

Zheng, G. Q., Ho, D. K., Elder, P. J., Stephens, R. E., Cottrell, C. E., & Cassady, J. M. (1994). Ohioensins and pallidisetins: Novel cytotoxic agents from the moss *Polytrichum pallidisetum. Journal of Natural Products*, *57*(1), 32–41. doi:10.1021/np50103a005 PMID:7512623

Section 4

Plant-Specific Pharmacological Utilizations

Chapter 15
Eupatorium birmanicum: A Medicinal Plant of Ritualistic Importance in the North-East Indian State of Manipur

Rubina Chongtham
Deshbandhu College, University of Delhi, India

Madhu Rani
https://orcid.org/0000-0001-8759-6852
Deshbandhu College, University of Delhi, India

ABSTRACT

Plants have been a source of treatment and a cure to various diseases and health conditions. India has immense traditional knowledge of useful plants of medicinal importance. This knowledge has been an intrinsic part of the lifestyles of various indigenous peoples in different parts of the country and has served as the basis of discovery/designing of modern medicines. One such region rich in traditional knowledge of medicinal plants is the north-east Indian state of Manipur. Eupatorium birmanicum DC known as Langthrei (Asteraceae), which is grown in every household and has a revered position, has anti-ulcer properties, and crushed fresh juice is taken orally to treat gastro-enteritis. There is an abundance of such ethnomedicinally important plants whose improved scientific understanding will improve their value in treating chronic conditions as well as conserving the plants and their knowledge. This chapter emphasizes the importance of E. birmanicum, discussing its various medicinal properties.

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INTRODUCTION

For centuries, indigenous plants have been an integral part of food as well as medicine in Manipur. It goes without saying that conserving and recording such traditional knowledge is of utmost importance, not only from a cultural and utilitarian perspective but also to prevent cases of bio-piracy. An important way to conserve plants of importance is through ritualistic and folk traditions. Such traditions reflect the commitment of indigenous peoples towards conservation of biodiversity and sustainable use of natural resources. The Meitei community of Manipur is one of the communities that have contributed in conservation of these plants by incorporating them into their religious practices and worship of nature. In fact, a systematic and elaborate tradition of folk medicine exists which is recorded as *Hidaklon* in five volumes of text. Various rituals involve offering of seven different flowers and seven different fruits as offering to the gods. Most of these plants have been found to have medicinal properties. Some of the plants are either offered to gods and ancestors as offerings, parts of the plant used as rosaries for protection against evil, used as fumigant to ward off evil spirits, etc. Though the folk use can be many a times seeped in superstitions or religious beliefs, never-the-less, these plants are also used as medicines.

There are several prominent examples. *E. birmanicum* grown in every household has anti-ulcer properties. The bark of *Erythrina variegata* Murr. (Fabaceae) is used to make rosaries for protection of the wearer and its twig is used to make a decoction that serves as liver tonic when mixed with honey. Another plant, *Cyperus rotundus* Linn. (Cyperaceae) is offered to the gods and also serves as anthelminthic to expel intestinal worms when consumed as juice. *Cedrela toona* Roxb. ex Rother (Meliaceae) is used in rituals to purify a house by dipping its twig in water and using it to sprinkle water around. Medicinally, the fresh leaf when boiled in water is used as bath water to cure poxes and other skin diseases. *Plectranthus terniflorus* (Vatke) Agnew (Lamiaceae) leaf is burnt to use as a fumigant to disinfect rooms, especially maternity rooms to protect both mother and babies from any pathogens. It is also used to cure fungal and bacterial diseases. Out of the wide range of plants known to this community; this chapter will explore the medicinal properties and uses of one of such plants used in rituals of the Meiteis, *Eupatorium birmanicum*.

E. birmanicum has several synonyms. Some of them are *Eupatorium allaisii*, *Eupatorium aregentum* Wallich, *Eupatorium cannabinum* subsp. *cannabinum*, *Eupatorium cannabinum* var. cannabinum, *Eupatorium cannabinum* var. indivism DC., *Eupatorium mairei, Eupatorium simonsii* C.B.Clarke, *Eupatorium trifidum* Vahl, *Eupatorium viscosum wallich, Chrone heterophylla* Dulac, etc. (The Plant List). It goes by the common English names, Burma agrimony, water hemp, hemp agrimony or hemp Eupatorium (USNPGS). It is called *Langthrei* in Manipuri.

Habit and Habitat of E. birmanicum

E. birmanicum is a widely distributed plant. It is found in several countries in Africa (Algeria, Morocco), Asia (Armenia, Russia, Iran, Iraq, Nepal, China, etc.), Europe (Estonia, Lithuania, Russia, Austria, Belgium, Germany, Hungary, Netherlands, Ireland, Spain, etc.), North America (Canada and USA) and Australia (USNPGS). In India, it is abundant in Manipur, where it forms an important part of rituals as well as folk medicine. It is often grown in homesteads for its importance. Situated in the north-eastern part of India, Manipur shares its eastern and southern borders with Myanmar and hence is a part of the Indo-Myanmar biodiversity hotspot. Manipur is a small state of 22,327 km^2 area lying between 23°80´N and 25°68´N latitudes and 93°03´E and 94°78´E longitudes. The state is mainly mountainous with mountain ranges surrounding a central valley with an area of 2230 km^2 covering just 10.02% of the total area. Here, *E. birmanicum* grows in wild as well as domesticated and is extensively used.

E. birmanicum is a perennial herb or under-shrub, whose height can range from about 50 cm to 150 cm. It has erect stem with simple or apical corymbose branching. It bears synflorescence branches and peduncles that are densely hairy. It has sessile/ shortly petilate, exstipulate, lanceolate leaves with serrated margin, a cuneate or broadly cuneate base and an acuminate or long acuminate apex. The leaves are borne in opposite and sometimes alternate fashion. The plant often grows in groups have straight, rarely branched cylindrical and glabrous stem. Its inflorescence head is a densely compound corymb and bear homogamous flowers. It bears numerous capitula with 3-7 flowers. The flowers have campanulate involucre with purple-red, pink or whitish corolla. The fruit is black or black-brown achene in colour and truncate with five ridges (Flora of China, http://www.efloras.org, Singh *et al.,* 2016).

Folk use of E. Birmanicum

Eupatorium has a wide use in folk medicine of Manipur amongst several tribes and hold a sacred place in the religious practice of the Meitei community. The parts of the plant that are mainly used for medicinal purposes are the leaves and young shoots. The juice extracted from the leaves or the fresh shoot directly is consumed to get relief from burning sensation in the mouth and stomach after consumption of chilies. The leaves are ingested, often in salads, to cure cough. A common practice of interest amongst the tribes of north-east India is dipping fresh buds of the plant in water and using it to sprinkle the water on epileptic persons to cure the disease (Sinha, 1996). In folk medicine, leaves of plant have been used to treat gastro-enteritis (Ningombam *et al.,* 2014). The anti-ulcer use of the plant by natives of Manipur

is supported by evidence showing chloroform extracts possessing potent anti-ulcer activity (Devi *et al.*, 2007).

There are reports of traditional and ethno-medicinal usage of *E. cannabinum* in other parts of the world as well. For instance, in Taiwan it is said to be used for treating diarrhea, diabetes, headache, hepatitis and hypertension. It is also said to be used in case of heavy menstrual bleeding, wherein an infusion made from tender leaves of Eupatorium is consumed orally once daily for five days. It is also known to be used as a remedy for cold, flu and fever. The juice of leaves and stem of the plant has been reported to be put directly on wounds to stop bleeding (Chang & Lin, 2003, Chiu & Chang, 2001, Gogoi & Zaman, 2013, Singh *et al.,* 2002).

Chemical Composition

E. cannabinum contains a number of sesqiterpene lactones- the major one being eupatoriopicrin, flavonoids, terpenoids, polyphenols, volatile oils, pyrrolizidine alkaloids, tannins, saponins and immunoactive polysaccharides (Dutta & Mahanta, 2016; Khare, 2007). Chen *et al.,* (2011) isolated 21 different chemical compounds from the leaves and stem of *E. cannabinum* that included thymol, benzofuranoid and phenylpropanoid derivatives (Chen *et al.,* 2011). Thymold have been isolated from roots as well (Chen *et al.,* 2014). Root cultures have been shown to yield as many as 7 benzofurans, which were isolated and identified (Siebertz, 1989). The subterranean portions of the plant have been shown to contain several pyrrolizidine alkaloids, such as lycopsamine, echinatine isomers and intermedine, and the beta-acyl, beta-angelyl/ tiglyl and beta-(iso)valeryl esters of some of the alkaloids. Out of these, those alkaloids having a saturated necine base trachelanthamine isomers and few beta-anglyl/tiglyl esters were found exclusively in roots (Edgar *et al.,* 1992; Hendriks *et al.,* 1987; Hendriks *et al.,* 1983). Aerial parts have been assessed to contain a total of 312.39 g/kg of various phenolic components consisting of the likes of chlorogenic acid, 3,5 dicaffeoylquinic acid, 4,5 dicaffeoylquinic acid, flavonoids, etc. (Fraisse *et al.,* 2011). Flavones, like 6-methoxyflavones hispidulin and eupafolin, and flavonol glycosides such as astragalin, kaempferol-3-rutinoside, hyperoside, isoquercitrin and rutin, have also been isolated from the leaves and stems of *E. cannabinum* (Elema *et al.,* 1989). Various essential oils have also been isolated from diverse parts of *E. cannabinum*. Amongst the compounds from various aerial parts, Germacrene D has been reported to be the most abundant, while others like germacrene B, valencene, β-caryophyllene, alphaphellandrene, α-farnesene, linoleic acid ethyl ester etc. might be present in varying amounts in plants of different subspecies or different regions (Mirza *et al.,* 2006; Paolini *et al.,* 2005; Senatore *et al.,* 2001; Mehdiyeva *et al.,* 2010). On the contrary, the essential oils from the roots of *E. cannabinum* has been found to contain large amounts of oxygenated compounds (61%), especially

oxygenated monoterpenes (54%). In the oil extracted from root, 106 components were identified, whose major components were reported to be monoterpenes esters (33%), neryl isobutyrate (17.6%), thymyl methyl oxide (15.1%), delta-2-carene (14.5%) and beta-pinene (5.7%) (Paolini *et al.,* 2007).

Antimicrobial Activity

Extracts of *E. cannabinum* in various solvents have been tested against different micro-organisms. Methanol and chloroform extracts of *E. birmanicum* has been shown to demonstrate inhibitory effect against three fungal species, viz., *Fusarium oxysporum, Curvularia lunata* and *Trichoderma viride*, albeit with different sensitivity (Devi *et al.,* 2007). In the same study, coumarin, β-sitosterol and β-sitosterol-D-glucoside were isolated from the chloroform extract; and *o*-coumaric acid, cerebroside, ceramide, and quercetin-3-*o*-rutinoside from the methanol extract of *E. birmanicum* leaves. Extracts of different solvents were also shown to have different levels of inhibitory effect in this study. This might indicate that the active principles of the plant have narrow antifungal spectrum.

The essential oil of *E. birmanicum* has also been used to study its antibacterial and antifungal effects. Fungicidal activity of *E. birmanicum* essential oil has been reported in *Aspergillus niger*, whereas it was found to be fungistatic against *Trichoderma lignorum* and *F. oxysporum* (Mehdiyeva *et al.,* 2010). The oil has been tested against various gram positive (*Staphylococcus aureus*, *Streptococcus faecalis*, *Bacillus subtilis* and *Bacillus cereus*) and gram negative (*Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichia coli* and *Salmonella typhi* Ty-2) bacteria. It showed considerable antimicrobial activity against all the bacteria that were tested in the study. It worked especially well against Gram positive bacteria, particularly *Streptococcus faecalis.* The highest resistance to the anti-microbial activity of the oil was observed in *P. aeruginosa* (Senatore *et al.,* 2001). In another study, *in vitro* tests were performed using the "drop agar diffusion" method to evaluate the effect of chloroform, hydroalcoholic and aqueous extracts of *E. cannabinum.* These tests were conducted against gram positive bacteria (*B. cereus*, *Staphylococcus aureus* and *Enterococcus faecalis*), gram negative bacteria (*Escherichia coli*) and fungi (*Candida albicans* and *Aspergillus niger*). Inhibitory effect was seen in *E. coli*, *B. cereus* and *C. albicans* with the chloroform and hydroalcoholic extracts. However, no inhibitory activity could be recorded against *S. aureus*, *E. faecalis* and *A.niger* (Purcaru *et al.,* 2015).

The aqueous extract of *E. birmanicum* has been tested against plant pathogenic fungus, *Drechslera oryzae* that causes brown leaf spot of rice. It was reported to have shown a 31% reduction in radial growth of mycelium of *D. oryzae* at 20% concentration (Devi & Chhetry, 2013). Thus, *Eupatorium* extracts in different

solvents have been tested against a host of microbes and have shown potential as an antimicrobial agent in both plant and animal systems.

Antiulcer Effects

As mentioned earlier, in folk medicine of Manipur, *E. birmanicum* is often used for treating stomach ulcers and to alleviate the burning sensation in stomach resulting from eating chilies (Singh et al, 2016). The leaves are consumed directly or an extract of the leaves is administered. An extract of the leaves is prepared in honey for the treatment of stomach ulcers (www.kiran.nic.in, ICAR). Not much research has been conducted to study the anti-ulcer activity of *E. birmanicum*, however there are reports of anti-ulcer properties of many other species of *Eupatorium*. For example, the efficacy of mixture of honey and the leaf extract has been experimentally shown in another *Eupatorium* species, *Chromolaena ororata*. Up to 72.67% inhibition of ethanol + HCl-induced gastric lesions was achieved by treating with a combination of aqueous extract and honey, whereas 58.92% inhibition was achieved by honey and ethanol extract (Nr Jannah *et al.,* 2006). The leaves of *E. nodiflorum* (also known as Tamu-Langthrei) have been used in treating stomach ulcer in the hills of Manipur (Devi et al, 2015). In another species of *Eupatorium*, *E. aschenbornianum*, Sánchez-Mendoza et al (2010) have been able to validate the use of the plant in treating gastric ulcer by isolating the gastroprotective principle, encecanescin. They demonstrated the anti-ulcer protective activity (85.65 ±4.76%) of hexane extract of the plant against ethanol-induced gastric ulcer in model rats. This protective action triggered by encecanescin could be attenuated by N(G)-nitro-L-arginine methyl ester, N-ethylmaleimide and indomethacin, thereby indicating the involvement of NO, prostaglandins and sulfydryl groups (Sánchez-Mendoza *et al.,* 2010). Krishnan *et al.,* (2014), reported that *E. triplinerve* extract contain some active agents that possess anti-ulcer effect against acetic acid-induced ulcerative colitis in the colon of mice that act by scavenging oxidative radicals and enhancing the cellular levels of antioxidant enzyme, Glutathione-s-transferase (GST), Gltathione peroxidase (GPx) and Catalase (CAT) at the ulcerated sites. Antiulcer activity was also reported in ethanol extract of *E. adenophorum* leaves (Mandal *et al.,* 2004).

Antiinflammatory Effects

Inflammation is marked by production of superoxide anion (O^{2-}) and neutrophil elastase activity. Several compounds isolated from the aerial parts of *E. birmanicum* have been reported to inhibit production of both superoxide anion and elastase, which might be an indication that these compounds are capable of countering inflammation and its adverse effects on the system. Chen *et al.,* (2011) isolated new compounds

(9-Acetoxy-8,10-epoxythymol 3-O-tiglate; 9-acetoxy8,10-dehydrothymol 3-O-tiglate, 9-acetoxythymol 3-O-tiglate; 8-methoxy-9-O-isobutyrylthymol; 10-acetoxy-8-hydroxy-9-O-angeloylthymol; and 1-(2- hydroxy- 4-(hydroxymethyl) phenyl)ethan-1-one) and demonstrated their inhibitory activity (IC_{50} value of 18.4 μM) against generation of superoxide anion (O^{2-}) by human neutrophils induced by fMLP/CB. Elastase release in respose to fMLP/CB was shown to be inhibited by *E. cannabinum* compounds, viz., 9- (3-Methylbutanoyl)-8, 10-dehydrothymol; eupatobenzofuran; 9-isobutyryloxy-8, 10- dehydrothymol; 10-acetoxy-8-hydroxy-9-Oangeloylthymol and 1-(2-hydroxy-4- (hydroxymethyl) phenyl) ethan-1-one (with IC_{50} value of 18.3 μM). In a study the antiinflammatory effect of flavonoids from another *Eupatorium* species, *E. arnottianum,* was elucidated. The isolation of three anti-inflammatory compounds namely, nepetin, jaceosidin and hispidulin from supporting its traditional use against inflammation (Clavin *et al.,* 2007).

Cytotoxic Effect

Various extracts of *E. birmanicum* and compounds (flavanoids, essential oils etc.) have been tested and reported to have cytotoxic effect on different cancer cell lines in a number of studies. Ethanolic extract of *E. birmanicum* was observed to be cytotoxic to colon cancer cell line HT29 without severe DNA damage. Upon testing various concentrations (0.5, 5, 25 and 50 μg/ml), significant reduction of HT29 cell viability was observed for 50 μg/ml extract after 24 h of exposure, while other concentrations (0.5, 5 and 25 μg/ml) after 96 h. Treatment with ethanolic extract of *E. birmanicum* at 25 μg/ml for 48h could induce permanent damage to the cells causing an extreme decline in cell viability even after a recovery period of 72h. Expression analysis was done on the cells treated with the 25 μg/ml extract for 48h. In the analysis, p21 was reported to have shown up-regulation whereas NCL, FOS and AURKA were down-regulated. This indicates a reduction in the capacity of the cells to proliferate. On the other hand, cytological analyses of the same sample revealed that the colony morphology was altered; H3K9 was hyperacetylated and a radical mitotic nuclear disruption was observed that denote an initiation of cell death. When the cells were treated with *E. birmanicum* ethanolic extract combined with chemotherapeutic agent, doxorubicin, and the co-exposure induced a decrease in cell viability in relation to doxorubicin for all *E. cannabinum* ethanolic extract concentrations, without affecting the doxorubicin-induced cell cycle arrest indicating a potential synergistic effect (Ribeiro-Varandas *et al.,* 2014). *E. birmanicum* contains a sesquiterpene lactone, eupatoriopicrin, which has shown cytotoxicity against different tumors. During in vitro cytotoxicity tests at concentrations ranging from 1.0–5.2 molar, eupatoriopicrin proved to be significantly cytotoxic against leukemia tumor and ZNS tumor cells (V 251) (Rucker *et al.,* 2001). An earlier study on the

effect of eupatoriopicrin on cancer cells in vitro (FIO 26 cells) and in vivo (FIO 26 and Lewis lung tumour-bearing mice), demonstrated its anticancer effect in terms of Glutathion (GSH) depletion. In the *in vitro* clonogenic assay using FIO 26 cells, IC_{50} for 1 h exposure to eupatoriopicrin was found to be 1.5 µg/ml (4.1 nmol/ml) and it caused the depletion of ~25% of its cellular GSH level. The cytotoxic effect of eupatoriopicrin was enhanced by pretreatment of the FIO 26 cells with buthioninesulphoximine (BSO), leading to more than 99% GSH depletion. The *in vivo* study of tumour growth delay in C57Bl mice with FIO 26 fibrosarcoma and Lewis lung carcinoma revealed growth inhibition of the tumours after i.v. injection of 20 or 40 mg/kg eupatoriopicrin, at a tumour volume of about 500 µL. Here also, significantly increased delay in tumour growth was observed upon pretreatment with BSO at a dose of 4 mmol/kg ip, 6 h before eupatoriopicrin treatment (Woerdenbag *et al.,* 1989). It has been noted that DNA damage may be associated with the cytotoxic effect of eupatoriopicrin. In an experiment done on Ehrlich ascites tumour cells, it was observed that when incubated for 2 h with eupatoriopicrin, the tumour cell, underwent DNA damage at concentrations higher than those causing cell death (1-10 µg/ml). BSO treatment that depleted GSH level by 99% could enhance the extent of DNA damage (Woerdenbag *et al.,* 1989). In another study, flavonoids isolated from the aerial parts of *E. birmanicum*, vizhispidulin, eupafolin and rutin, were reported to be cytotoxic against Ehrlich Ascites tumour (Elema *et al.,* 1989). Various concentrations of hydroalcoholic extract of *E. birmanicum* (ranging from 7 to 500 µg/ml) were used to perform MTS assays to test viability of Jurkat cells at 24 and 48 h. It was observed that growth was significantly inhibited in a dose and time-dependent manner. The IC_{50} value of the extract was 73.3 µg/ml at 48 hours (Ionita *et al.,* 2013). Various compounds have been isolated from *E. birmanicum* and tested for their cytotoxicity. Among them thymol derivatives (9-acetoxy-8,10-epoxythymol 3-O-tiglate) was the most cytotoxic with IC_{50} values of 0.02 ± 0.01, 1.02 ± 0.07, and 1.36 ± 0.12 µg/ml, respectively, against DLD-1, CCRF-CEM, and HL-60 cell lines. Eupatobenzofuran and 10- acetoxy-9-O-angeloyl-8-hydroxythymol exhibited cytotoxicities, with IC_{50} values of 2.63 ± 0.22 and 1.14 ± 0.16, and 2.31 ± 0.14 and 7.63 ± 0.94 µg/ml, respectively, against DLD-1 and CCRF-CEM cell lines (Chen *et al.,* 2014).

In another study done to investigate the pharmacological properties of *E. cannabinum* essential oils. Judzentiene *et al.,* (2016) isolated various essential oils from different Lithuanian wild populations of *E. cannabinum* and classified them according to the most dominant component. Then cytotoxicity tests were performed using brine shrimp (*Artemia* sp.) assay, which showed that the essential oil samples with germacrene D and neryl acetate as the predominant components were found to be particularly toxic with LC_{50} value determined as 16.3-22.0 µg/ml (Judzentiene *et al.,* 2016).

Choleretic and Hepatoprotective Effects

There are reports that suggest potential choleretic and hepatoprotective effects of the plant. Lexa *et al.,* (1989) evaluated the influence of aqueous extract of *Eupatorium* on bile production by determining quantity of bile flow, bile acids output, and (14C)-erythritolclearance using *in vivo* rat models. Various doses of aqueous extract of the plant (125, 250, 500, 1000 mg/kg) were injected into rats. The study reported that significant increase in bile flow was observed after a single injection, reaching maximum efficiency within 30 to 90 mm (19% at 250 mg/kg). They also determined the anti-hepatotoxic efficacy of *E. cannabinum* in CCl_4-induced hepatotoxicity model rats. The extract demonstrated anti-necrotic properties. Pretreatment with *E. cannabinum* 30 min before $CC1_4$ treatment significantly decreased the level of GPT at 250, 500, and 1000 mg/kg (Lexa *et al.,* 1989). Such antinecrotic activity against carbon tetrachloride-induced hepatotoxicity in rats was attributed to the flavonoids (viz, rutoside, hyperoside and quercetin) and phenolic acids present in the plant and not due to the presence of eupatoriopicrin. Other compounds in the plant, like acrylic, lactic, malic and citric acids have been reported to show protective effect against acute ethanol induced toxicity in mice (Khare, 2007).

Though more detailed studies on chloretic and hepatoprotective action of *E. cannabinum* is lacking, however, other species of *Eupatorium* have been reported to have different effects on the liver. *Agrimonia eupatoria* or common agrimony has been identified as a cholagogue, which means it is capable of increasing flow and release of stored bile from the gall bladder (Leah Hechtman, Clinical Naturopathic Medicine, Elsevier). Gorzalczany *et al.,* (2008) had reported *E. buniifolium*, an herb widely used in Argentine folk medicine to address hepato-biliary complaints, that it exhibited chloretic effect. Upon both oral (500 mg/kg) and intravenous (250 mg/kg) administration of aqueous extract of *E. buniifoliuum*, a significant chloretic effect was observed. However, the treatment did not show any changes in bile output (Gorzalczany *et al.,* 2008).

Insecticidal and Repellent Effect

Apart from the health benefits and the medicinal properties of the plant, it also possesses insecticidal and repellant effects against pests and insects. Singh *et al.,* (2015) reported the efficiency of methanol and chloroform fraction of *E. cannabinum* in controlling *Callosobruchus chinensis*. The extracts exhibited maximum repellent activity (90%) at a concentration of 250ppm. *E. cannabinum* has been found to be toxic against the second and fourth instars of *Culex quinquefasciatus* and *Aedes aegypti* at concentrations ranging from 20 to 50 ppm and the effect was shown to be dose dependent. The IC_{50} values for the 100 ppm of purified fraction against

second and fourth instars of *A. aegypti* were observed to be 40.11 and 34.10 ppm respectively (Dar *et al.,* 2013).

Anticonvulsant Activity

As mentioned earlier, *E. birmanicum* plant has been used in folk medicine to treat epileptic seizure. Babycha & Valte (2018) have provided supporting evidence for anticonvulsant activity of the plant in mice model. In their study, they used aqueous extract of the plant by itself and in combination with ethosuximide against seizure induced by pentylenetetrazole (PTZ) in albino mice. They demonstrated that at dosage 200, 400 & 800 mg/kg, *E. birmanicum* extract significantly delayed the onset of convulsions post-PTZ-treatment ($p<0.001$).

Antioxidant Effect

The antioxidant effect of hydro-alcoholic extract of *E. cannabinum* (at doses of 0.1-10mg/ml) and EC_{50} of the extract was determined at 2.91mg/ml by DPPH antioxidant assay (Ionita *et al.,* 2013). The antioxidant activities of caffeoyl derivatives isolated from the aerial parts were; chlorogenic acid (EC_{50} = (13.80 ±0.36) µmol/l), 3,5-dicaffeoylquinic acid (EC_{50} = (7.62 ± 0.22) µmol/l), 1,5-dicaffeoylquinic acid (EC_{50} = (7.85 ±0.23 µmol/l) and 4,5-dicaffeoylquinic acid (EC_{50} = (7.99 ±0.31 µmol/l) (Fraisse *et al.,* 2011).

Antidiabetic Activity

The leaves extract of the plant has been shown to exert significant anti-hyperglycemic effect in alloxanized rabbits possibly by pancreatic cells stimulating action as the plant was found effective in only mild to moderate and not in severe diabetes (Puri & Baral, 1998).

Immunological Effects

The polysaccharides isolated from the alkaline aqueous extract of *E. cannabinum* showed a phagocytosis enhancing effect as determined in three immunological test systems (carbon clearance, granulocyte- and chemiluminescence test) (Vollmar *et al.,* 1986). Polysaccharide fractions were isolated from the aqueous and alcaline-aqueous extracts of *E. cannabinum* showed significant immunostimulating activities in granulocytes- and carbon clearance tests (Wagner *et al.,* 1986).

Anti-Necrotic Activity

The aqueous extract of *E. cannabinum* possessed anti-necrotic properties against CC14-induced hepatotoxicity. Pretreatment (30 min before CC14), with *E. cannabinum* showed a significant decrease of GPT levels (at 250, 500, and 1000 mg/kg) using CCl4 in *in vivo* model in rats (Lexa *et al.,* 1989).

CONCLUSION

Traditional knowledge is an ocean of information that forms a resource for new drug discovery and drug design. Exploring them and recording known practices about them is of extreme importance, not only to have an inventory of our vast knowledge of plant uses but also to contribute in the conservation of biodiversity. It has to be emphasized that successful efforts to conserve biodiversity go hand-in-hand in recognizing the role of traditional knowledge and the indigenous tribes who hold such knowledge. It should also be mentioned here that exploring and compiling such information will go a long way in avoiding cases of bio-piracy. India has several biodiversity regions, one of which is the North-eastern region. Manipur is a north-eastern state which has a rich tradition in medicinal plants. However, traditional knowledge of this part of the country is largely absent from the over-all discourse on Indian traditional plants such as those laid down in medicinal systems of Ayurveda, Unani, etc. Therefore effort must be made to actively explore and include plants used traditionally in this region. A fine example is *E. birmanicum*, which is often regarded as a weed in larger parts of its growth, occupies a revered position in the folk practices of Manipur. It being a ritualistically important plant ensures its conservation and its profound usage as a medicinal plant. Its folk traditional usage has been extensively investigated using various assay techniques. This has shed light on the scientific reasons behind much of its usage. This might lead to the development of drugs of therapeutic importance.

REFERENCES

Babycha, L., Devi, L. T., Singh, O. J., & Valte, V. (2013). The anticonvulsant effect of *Eupatorium birmanicum* DC leave extract alone and in combination with lamotrigine against MES seizure in albino mice. *Journal of Evolution of Medical and Dental Sciences*, *2*(38), 7250–7255. doi:10.14260/jemds/1288

Babycha, L., & Valte, V. (2018). Anticonvulsant activity of aqueous extract of *Eupatorium birmanicum* DC. Leaves on seizure induced by PTZ in albino mice, alone and in combination with ethosuximide. *International Journal of Pharmaceutical Sciences and Research*, *9*(5), 2048–2052.

Chang, Y. S., & Lin, I. H. (2003). Compendium of medicinal plants used by the indigenous people of Taiwan. Department of Health, Executive Yuan, Taipei, Taiwan.

Chen, J. J., Tsai, Y. C., Hwang, T. L., & Wang, T. C. (2011). Thymol, benzofuranoid, and phenylpropanoid derivatives: Anti-inflammatory constituents from *Eupatorium cannabinum*. *Journal of Natural Products*, *74*(5), 1021–1027. doi:10.1021/np100923z PMID:21391659

Chen, L. C., Lee, T. H., Sung, P. J., Shu, C. W., Lim, Y. P., Cheng, M. J., ... Chen, J. J. (2014). New thymol derivatives and cytotoxic constituents from the root of *Eupatorium cannabinum* ssp. *asiaticum*. *Chemistry & Biodiversity*, *11*(9), 1374–1380. doi:10.1002/cbdv.201300392 PMID:25238078

Chiu, N. Y., & Chang, K. H. (2001). The illustrated medicinal plants of Taiwan. SMC Publishing Inc.

Clavin, M., Gorzalczany, S., Macho, A., Munoz, E., Ferraro, G., Acevedo, C., & Martino, V. (2007). Anti-inflammatory activity of flavonoids from *Eupatorium arnottianum*. *Journal of Ethnopharmacology*, *112*(3), 585–589. doi:10.1016/j.jep.2007.04.007 PMID:17570627

Dar, A. I., Saxena, R. C., Matadeen, B., Barela, B., & Jadhaw, V. (2013). Toxicity of *Eupatorium cannabinum* L. against second and fourth instar larvae of *Culex quinquefasciatus* and *Aedes aegypti*. *International Journal of Research in Ayurveda and Pharmacy*, *4*(1), 63–66. doi:10.7897/2277-4343.04126

Devi, L. R., Singh, T. S., & Laitonjam, W. S. (2007). Antifungal and phytochemical studies of *Eupatorium birmanicum* DC. *Indian Journal of Chemistry*, *46B*, 1868–1872.

Devi, O. J., & Chhetry, G. K. N. (2013). Evaluation of antifungal properties of certain plants against *Drechslera oryzae* causing brown leaf spot of rice in Manipur valley. *International Journal of Scientific and Research Publications*, *3*(5), 1.

Devi, T. H. I., Devi, K. H. U., & Singh, E. J. (2015). Wild medicinal plants in the hill of Manipur, India: A traditional therapeutic potential. *International Journal of Scientific and Research Publications*, *5*(6), 1–9.

Dutta, B., & Mahanta, B. (2016). Studies on secondary metabolites, total phenol and flavonoid contents of *Eupatorium cannabinum* L. in Assam, India. *Journal of Medicinal Plants Studies*, *4*(2), 130–133.

Edgar, J. A., Lin, H. J., Kumana, C. R., & Ng, M. M. (1992). Pyrrolizidine alkaloid composition of three Chinese medicinal herbs, *Eupatorium cannabinum, E. japonicum* and *Crotalaria assamica. The American Journal of Chinese Medicine*, *20*(3-4), 281–288. doi:10.1142/S0192415X92000291 PMID:1471612

Elema, E. T., Schripsema, J., & Malingrd, T. M. (1989). Flavones and flavonol glycosides from *Eupatorium cannabinum* L. *Pharmaceutisch Weekblad Sci*, *11*(5), 161–164. doi:10.1007/BF01959464 PMID:2594467

Flora of China. (n.d.). *Eupatorium cannabinum*. Error! Hyperlink reference not valid..aspx?flora_id=2&taxon_id=200023930

Fraisse, D., Felgines, C., Texier, O., & Lamaison, J. L. (2011). Caffeoyl derivatives: Major antioxidant compounds of some wild herbs of the Asteraceae family. *Food and Nutrition Sciences*, *2*(03), 181–192. doi:10.4236/fns.2011.230025

Gogoi, B., & Zaman, K. (2013). Phytochemical constituents of some medicinal plant species used in recipe during 'Bohag Bihu' in Assam. *Journal of Pharmacognosy and Phytochemistry*, *2*(2), 30–40.

Gorzalczany, S., Muschietti, L., Repetto, M., & Kartin, L. (2008). Chloretic and antioxidant effect of *Eupatorium buniifolium. Pharmacologyonline*, *1*, 139–147.

Hendriks, H., Balraadjsing, W., Huizing, H. J., & Bruins, A. P. (1987). Investigation into the presence of pyrrolizidine alkaloids in *Eupatorium cannabinum* by means of positive and negative ion chemical ionization GC-MS. *Planta Medica*, *53*(5), 456–461. doi:10.1055-2006-962772 PMID:17269067

Hendriks, H., Malingré, T. M., & Elema, E. T. (1983). Pyrrolizidine alkaloids, flavonoids and volatile compounds in the genus Eupatorium. *Eupatorium cannabinum* L., an ancient drug with new perspectives. *Pharmaceutisch Weekblad. Scientific Edition*, *5*(6), 281–286. doi:10.1007/BF02074855 PMID:6364036

Ionita, L., Grigore, A., Pirvu, L., Draghici, E., Bubueanu, C., Ionita, C., ... Dobre, N. (2013). Pharmacological activity of a *Eupatorium cannabinum* L. extract. *Romanian Biotechnological Letters*, *18*(6), 8779–8786.

ITIS. (n.d.). *Eupatorium cannabinuz.* https://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN& search _ value =35984

Judzentiene, A., Garjonyte, R., & Budiene, J. (2016). Variability, toxicity, and antioxidant activity of *Eupatorium cannabinum* (hemp agrimony) essential oils. *Pharmaceutical Biology*, *54*(6), 945–953. doi:10.3109/13880209.2015.1078384 PMID:26439817

Khare, C. P. (2007). *Indian medicinal plants: an illustrated dictionary*. New York: Springer-Verlag. doi:10.1007/978-0-387-70638-2

Krishnan, M., Jayaraj, R., Megala, J., & Namasivayam, E. (2014). Antioxidant mediated antiulcer effect of *Eupatorium triplinerve* Vahl against acetic acid induced ulcerative colitis in mice. *Biomedicine & Aging Pathology*, *4*(2), 153–160. doi:10.1016/j.biomag.2013.12.002

Lexa, A., Fleurentins, J., Lehr, P. R., Mortier, F., Pruvost, M., & Pelt, J. M. (1989). Choleretic and hepatoprotective properties of *Eupatorium cannabinum* in the rat. *Planta Medica*, *55*(02), 127–132. doi:10.1055-2006-961904 PMID:2748727

Mandal, S. K., Mandal, S. C., Pal, M., & Syr, T. (2004). Antiulcer activity of ethanol extract of *Eupatorium adenophorum* leaf. *Indian J. Nat. Prod.*, *20*(2), 23–25.

Mehdiyeva, N. P., Serkerov, S. V., & Bahshaliyeva, K. F. (2010). Chemical composition and antifungal activities of the essential oils of from the flora Azerbaijan. *Chemistry of Plant Raw Material*, *2*, 139–142.

Mirza, M., Navaei, M. N., & Dini, M. (2006). Volatile constituents of essential oils isolated from flowers and leaves of *Eupatorium cannabinum* L. from Iran. *Iranian Journal of Pharmaceutical Research*, *2*, 149–152.

Ningombam, D. S., Devi, S. P., Singh, P. K., Pinokiyo, A., & Thongam, B. (2014). Documentation and assessment on knowledge of ethno-medicinal practitioners- a case study on local Meetei healers of Manipur. *IOSR Journal of Pharmacy and Biological Sciences*, *9*(1), 53–70. doi:10.9790/3008-09115370

Nur Jannah, M. H., Mahmood, A. A., Sidik, K., & Salman, I. (2006). Cytoprotective effects of honey in combination with aqueous and ethanol extracts from *Chromolaena odorata* L. (*Eupatorium odoratum* L.) in rats. *Journal of Health and Translational Medicine*, *9*(1), 7–13. doi:10.22452/jummec.vol9no1.3

Paolini, J., Costa, J., & Bernardini, A. F. (2005). Analysis of the essential oil from aerial parts of *Eupatorium cannabinum* subsp. *corsicum* (L.) by gas chromatography with electron impact and chemical ionization mass spectrometry. *Journal of Chromatography. A*, *1076*(1-2), 170–178. doi:10.1016/j.chroma.2005.03.131 PMID:15974084

Paolini, J., Costa, J., & Bernardini, A. F. (2007). Analysis of the essential oil from the roots of *Eupatorium cannabinum* subsp. corsicum (L.) by GC, GC-MS and 13C-NMR. *Phytochemical Analysis*, *18*(3), 235–244. doi:10.1002/pca.977 PMID:17500367

Purcaru, T., Alecu, A., Diguta, C., & Matei, F. (2015). *In vitro* evaluation of *Eupatorium cannabium* antimicrobial activity. *AgroLife Scientific Journal*, *4*(2), 92–97.

Puri, D., & Baral, N. (1998). Hypoglycemic effect of *Biophytum sensitivum* in the alloxan diabetic rabbits. *Indian Journal of Physiology and Pharmacology*, *42*, 401–406. PMID:9741656

Ribeiro-Varandas, E., Ressureição, F., Viegas, W., & Delgado, M. (2014). Cytotoxicity of *Eupatorium cannabinum* L. extracts against colon cancer cells and interactions with bisphenol A and doxorubicin. *BMC Complementary and Alternative Medicine*, *14*(1), 264. doi:10.1186/1472-6882-14-264 PMID:25056133

Rucker, G., Heiden, K., & Schenkel, E. (2001). Antitumor-active lactones from *Kaunia rufescens* and *Eupatorium cannabinum. Journal of the Indian Institute of Science*, *81*, 333–334.

Sánchez-Mendoza, M. E., Reyes-Trejo, B., Sánchez-Gómez, P., Rodríguez-Silverio, J., Castillo-Henkel, C., Cervantes-Cuevas, H., & Arrieta, J. (2010). Bioassay-guided isolation of an anti-ulcer chromene from *Eupatorium aschenbornianum*: Role of nitric oxide, prostaglandins and sulfhydryls. *Fitoterapia*, *81*(1), 66–71. doi:10.1016/j.fitote.2009.07.009 PMID:19651191

Senatore, F., De Fusco, R., & Napplitano, F. (2001). *Eupatorium cannabinum* L. ssp. *cannabinum* (Asteraceae) essential oils. Chemical composition and antibacterial activity. *The Journal of Essential Oil Research*, *13*(6), 463–466. doi:10.1080/10412905.2001.9699730

Siebertz, R., Proksch, P., Wray, V., & Witte, L. (1989). Accumulation and biosynthesis of benzofurans in root cultures of *Eupatorium cannabinum. Phytochemistry*, *28*(3), 789–793. doi:10.1016/0031-9422(89)80116-5

Singh, H. B., Prasad, P., & Rai, L. K. (2002). Folk medicinal plants in the Sikkim Himalayas of India. *Asian Folklore Studies*, *61*(2), 295–310. doi:10.2307/1178975

Singh, M., Saxena, A. & Neeraj, P.K. (2015). Study of the larvicidal effect of *Eupatorium cannabinum* Linn (Family Asteraceae) leaf extract on *Callosobruchus chinensis* Linn (Family Bruchidae). *International Interdisciplinary Research Journal,* S42-50.

Singh, T. Th., Devi, A. R., Sharma, H. R., & Sharma, M. H. (2016). Plants used in the treatment of stomach problems by the scheduled caste community of Andro village in Imphal East District, Manipur, India. *International Journal of Current Research and Academic Review*, *4*(1), 23–38. doi:10.20546/ijcrar.2016.401.003

Sinha, S. C. & Mass. (1996). *Medicinal Plants of Manipur*. In Manipur Cultural Integration Conference, Imphal, Manipur, India.

U.S. National Plant Germplasm System. (n.d.). *Taxon: Eupatorium cannabinum L.* https://npgsweb.arsgrin.gov/gringlobal/taxonomydetail.aspx?315553

Vollmar, A., Schfer, W., & Wagner, H. (1989). Immunologically active polysaccharides of *Eupatorium cannabinum* and *Eupatorium perfoliatum. Phytochemistry*, *25*(2), 377–381. doi:10.1016/S0031-9422(00)85484-9

Wagner, H., Proksch, A., Riess-Maurer, I., Vollmar, A., Odenthal, S., Stuppner, H., ... Heur, Y. H. (1984). Immunostimulant action of polysaccharides (heteroglycans) from higher plants. *Arzneimittel-Forschung*, *34*(6), 659–661. PMID:6541484

Woerdenbag, H. J., Lemstra, W., Malingre, T. M., & Konings, A. W. (1989). Enhanced cytostatic activity of the sesquiterpene lactone eupatoriopicrin by glutathione depletion. *British Journal of Cancer*, *59*(1), 68–75. doi:10.1038/bjc.1989.13 PMID:2757925

Chapter 16
Therapeutic Importance and Application of Boswellic Acid From the Plant *Boswellia serrata*

Raghunath Satpathy
https://orcid.org/0000-0001-5296-8492
School of Biotechnology, Gangadhar Meher University, Sambalpar, India

ABSTRACT

Traditionally, the gum resin produced from the Boswellia serrata plant has been used in as a therapeutical compound. The gum that contains a chemical known as boswellic acid, AKBA (3-O-acetyl-11 keto-β-boswellic acid), and widely in ayurvedic medicines. This is used to treat the disease like reduction in various inflammatory conditions of the skin, eye, as well as respiratory disorders such as asthma, bronchitis, and laryngitis. The boswellic acids were also found capable to inhibit both hemolysis and chemotaxis of leukocytes and were shown to work by inhibiting C3-convertase, a key enzyme of the classical complementary pathway. In addition to this, the compound shows beneficial effects in various pharmacological properties like immunomodulation activity, polyarthritis, activity against Hepatitis C-virus and other harmful microbes, Colitis and Crohn's disease, and so on. The boswellic acid is also used to treat patients with memory disorders. In this chapter, the chemical nature and isolation of boswellic acid and its therapeutic importance have been highlighted.

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INTRODUCTION

The ecosystems of the earth are rich in biodiversity consisting of both plants and animals groups that make other form of life dependent on each other. From the ancient age, the human has relied on natural products especially from the plants to maintain good health by fighting with sickness, pain, and disease. The current allopathic medicines are having many side effects, therefore due to greater awareness in many cases, the allopathic medicines are replaced by the herbal traditional drugs. In the current scenario, there is a search in worldwide to obtain a novel therapeutically important plant product is considered as eco-friendly, non-toxic and economically viable to be used against various harmful diseases (Hoareau & DaSilva, 1999; Cordell, 2000). A plant usually produces two types of metabolites such as primary metabolites, the substances can be used subsequently in metabolic pathways and directly entered to the growth and metabolism process of the organism e.g. carbohydrates, proteins, and lipids. On the other hand the secondary metabolites do not enter to the normal growth and metabolism, however widely used for the defence mechanism in case of plants against the predators, parasites, and diseases (Said *et al.,* 2002; Arora *et al.,* 2005).

Boswellia Serrata Roxb (Burseraceae)

B. serrata is native to both Pakistan and India. The tree having the average height of 9-15 m and a diameter of 40-60 cm. The flowers greyish in nature. Flowering occurs during February to April and the ripening of the fruit occurs in the month of May to June. The flower colour is whitish in nature and each fruit bears three seeds. The product of the plant is boswellic acid, chemically consists of aromatic, multi-ringed organic compounds that contribute to anti-rheumatic properties has been studied. Also, the boswellic acids inhibit the enzyme 5-lipoxygenase, which is a key enzyme for the production and formation of leukotrienes in the body. Therefore this compounds is having anti-inflammatory responses hence used against the critical illnesses such as arthritis and asthma. The extract of the plant gum resin consists of three types of compounds, viz. terpenoids, essential oils, and gum. However, the active constituents in *Boswellia* are terpenoid and boswellic acids that corresponds to 37.5–65% of the total extract. Since from the ancient times, the natural resin product of plant are collected and used to produce the gum resin, popularly known as olibanum. The gum resin is usually harvested by making a cut on the trunk of the plant (Singh & Atal, 1986; Al-Harrasi *et al.,* 2014; Ahmed *et al.,* 2014).

This chapter deals with the experimental methods for characterization of boswellic acid and its potential therapeutic nature and application including, anticancer and

tumour agent, curing of chronic inflammatory disease and the mechanism behind it by narrating the literature.

CHEMISTRY OF BOSWELLIC ACID

The molecular feature of boswellic acids consists of a series of pentacyclic triterpene molecules that are produced as resins that constitute about 30% of the whole resin in the plant *B. serrata* and also contains a carboxyl group having the stoichiometric composition as $C_{30}H_{48}O_3$ (Mannino *et al.,* 2016). Boswellic acid may remain in the form of alpha boswellic acid and beta boswellic acid, also both these structures contains an extra hydroxyl group and different from one another by their triterpene structure. Basically, the gum is composed of carbohydrates (arabinose with small amount of xylose and galactose). As discussed in above section, the active components contains usually ~ 1.0% of acetyl-11-keto-β boswellic acid (AKBA).

Table 1. Molecular summary of Boswellic acid

S.N	Features	Description
1	Common Name	Boswellic acid
2	Chemical Name	beta-boswellic acid
3	IUPAC Name	(3R,4R,4aR,6aR,6bS,8aR,11R,12S,12aR,14aR,14bR)-3-hydroxy-4,6a,6b,8a,11,12, 14b-heptamethyl-2,3,4a,5,6,7,8,9,10,11,12,12a,14, 14a-tetradecahydro-1H-picene-4-carboxylic acid
4	SMILES format	CC1CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C(=O)O)O)C)C)C2C1C)C)C
5	Molecular Formula	$C_{30}H_{48}O_3$
6	Molecular Weight (g/mol)	456.70032
7	Partition coefficient (XLogP3-AA)	8.3

IDENTIFICATION AND QUANTIFICATION OF BOSWELLIC ACID

The following basic steps can be used to isolate and quantify the boswellic acids as described by Singh *et al.,* (2008).

- The gum resins of *B. serrata* are initially grinded into powder form and then used for all extraction procedures. Also, alternatively, the pure standards of boswellic acids can be purchased from outside for the quantification purpose used in the preparation of the standard curve.

- Solvent extraction process of *B. serrata* gum resins can be performed with the solvent methanol (with the extraction ratio 1:10 w/v).
- Then the orbital shaker is used to keep the extracted samples for a duration of five days in the dark condition and then filtered followed by rinsing of resins with methanol.
- Further, the extracted samples then concentrated by vacuum evaporation method, followed by drying in an oven at 70 °C for 4 h.
- Then the powdered extracts are stored at room temperature in the dark till the further chemical analysis.
- Finally, the boswellic acids are extracted and the quantification is performed by HPLC (High performance liquid chromatography) coupled to MS (mass spectroscopy) techniques.

Based on the extraction procedure, the extracts have been classified into three different categories such as: first type: it is the *alcoholic extract* of *B. serrata* and reported to inhibit inflammatory and arthritic activities. The second type: in this case the extract type is called *non-phenolic fraction* and this usually shows analgesic and some psychopharmacological effects as well as also anti-diabetic activity in rats. Similarly, the third type: this extract contains the essential oil is a mixture of monoterpenes, diterpenes, and sesquiterpenes. Gum part of the drug contains pentose and hexose sugars with some oxidizing and digestive enzymes. However, the resin portion of salaiguggal is composed of pentacyclictriterpene acid of boswellic acid is considered as the active component has been described by many researchers (Safayhi *et al.,* 1992; Qurishi *et al.,* 2010).

MEDICINAL IMPORTANCE OF BOSWELLIC ACIDS

Since the time immense *B. serrata* plant products has been used for the treatment of arthritis. The other medicated properties of this product has include the anti-inflammatory action as that of the action of conventional non-steroidal anti-inflammatory drugs (NSAIDs) (Ammon, 2010). Boswellic acid also inhibits inflammatory responses in the body by inhibiting the production of leukotriene via interaction with 5-lipoxygenase enzyme. Also, it has been observed from research that the long-term use of boswellic acid does not contribute any kind of harmful activity such as irritation, ulcer creation of the stomach (Ammon, 2002). Recent studies also clarified about the therapeutic activities of boswellic acids, which is significant in the treatment of diseases like cancer, microbial infection and immune response related activity. In addition to this, it also exhibits the analgesic, antipyretic,

and platelet-inhibitory actions (Abdel-Tawab *et al.,* 2011). The various specific therapeutically applications of the boswellic acid are described.

Potential Anticancer Activity of boswellic Acid

The inhibitory action against neoplastic activity, especially on brain tumors indicates about the efficacy of the boswellic acid. Several studies by researchers suggest that the component 3-O-acetyl-11-beta-boswellic acid (AKBA) of boswellic acids having the anti-carcinogenic effects (Roy *et al.,* 2016; Liu & Duan, 2009). The inhibitory action against tumor growth by the acetyl-11-Keto-β-boswellic acid has been studied and the mechanism responsible for the phenomena is by suppressing the Vascular Endothelial Growth Factor (VEGF) and the enzyme 5-Lipoxygenase, therefore proves its activity against the angiogenesis also colorectal cancer (CRC) (Jing *et al.,* 1999; Takahashi *et al.,* 2012). Acetyl-11-keto-β-Boswellic acid is also involved in decreasing the occurrence of pancreatic cancer cells by decreasing the expression of chemokine receptor gene. This effect is followed by the inhibition of the synthesis of DNA, RNA and protein in human leukemia HL-60 cells was studied whenever the AKBA is administered in a dose-dependent manner (Shao *et al.,* 1998; Park *et al.,* 2011).

It has been observed that the boswellic acid is quite effective for treating the patients having the brain tumors that further gives rise to the cerebral edema without any side effects (Kirste *et al.,* 2011). Similarly, boswellic acid was observed as an inhibitor of anti-prostate cancer activity (Xiufeng *et al.,* 2009).

Boswellic Acids in Chronic Inflammatory Disease

B. serrata extract also showed its anti-inflammatory activity during the animal experiments. The most evident action was observed as its activity in the inhibition of 5-lipoxygenase enzyme in addition to influencing the production of other molecules such as cytokines (interleukins and TNF-alpha) also interferes of the activation of complement system (Ammon, 2006; Ammon *et al.,* 1993). From the methanolic fraction of the *Boswellia* resin, the triterpene acids are isolated and identified to be inhibitory against 12-O-tetradecanoyl phorbol-13-acetate (TPA) causes inflammation, hence exhibits the anti-inflammatory activity (Banno *et al.,* 2006). Researchers revealed the synergistic effect of these compound mixture with glucosamine for the both anti-inflammatory and anti-arthritic activities in rats (Liu *et al.,* 2002). Boswellic acid was identified as an effective drug against the patients suffered from chronic colitis that is characterized by the symptoms like pain in the lower abdominal part of the body, rectal bleeding, diarrhoea also show sigmoid colon. Actually, the inflammatory phenomena involved in the colitis disease is due to increased

production of leukotriene compound. This leads to the enhanced chemotaxis and chemokinesis, followed by synthesis of superoxide radicals, hence helps in release of the lysosomal enzymes by the process of phagocytes. The boswellic acid was observed as act as a non-competitive inhibitor to the key enzyme 5-lipoxygenase and inhibits of the enzymatic actions (Gupta *et al.,* 1997).

Boswellic Acid as an Antidiarrheal Agent

Clinical studies suggested that, the *B. serrata* extract is responsible for the reduction of diarrhoea in patients suffered from inflammatory bowel disease. The mechanism of prevention of diarrhoea was identified that, the boswellic acid having a direct effect on it as it inhibits the intestinal motility that involves the Calcium ion (Ca^{2+}) channels (Borrelli *et al.,* 2006).

Activity Against Oral Cavity Pathogens

The boswellic acid showed the potential antimicrobial activities against oral cavity pathogens has been identified. Particularly, the effect of Acetyl-11-keto-β-boswellic acid (AKBA) was observed as having the antibacterial activity and the same has been evaluated by different methods of study such as time kill studies of pathogen, mutation prevention frequency test, post-antibiotic effect (PAE) and biofilm susceptibility assay against oral cavity pathogens (Raja *et al.,* 2011).

Antiasthmatic Effect

The gum resin of *B. serrata* that contains boswellic acids that have been shown to inhibit leukotriene biosynthesis as stated above. The gum resin was used (with a dose of 300 mg daily three times for a period of 6 weeks) to treat in case of a group of patients suffered from chronic bronchial asthma indicates a positive effect of the compound in the treatment of bronchial asthma (Gupta *et al.,* 1998).

Immuno Modulatory Effect

Usually, the extracted version of gum resin of *B. serrata* contains about 60% acetyl 11-keto beta boswellic acid (AKBA) along with other similar components such as 11-keto beta-boswellic acid (KBA), acetyl beta-boswellic acid. So, the effect of these beta boswellic acid has been evaluated for the anti-anaphylactic and mast cell stabilizing activity in its purified form that exhibits the immuno modulatory effect (Pungle *et al.,* 2003; Wildfeuer *et al.,* 1998).

Treatment of Crohn's Disease

The clinical trial was conducted to study the effect of *B. serrata* extract H15 with mesalazine in a comparative manner for the treatment of active Crohn's disease. It was observed that *B. serrata* extract H15 shows significant clinical efficacy for the treatment of Crohn's disease (Gerhardt *et al.* 2001).

Hypolipidemic, Hepatoprotection and Hypoglycemic Activity

In an experiment, the extract contains water soluble fraction of *B. serrata* was observed to be associated with decreasing of total cholesterol up to 48% and increased in High density Lipoproteins (HDL) in rats thereby proving its hypolipidemic potential (Zutshi *et al.,*1986). Similarly, the alcoholic extract of gum resin also proved its effect has hepatoprotective in nature that inhibits the galactosamine induced liver damage in mice by reducing aminotransferase and serum enzymes (Gerlach & Hiby, 1974). In addition to this, the formulation of *B. serrata* gum resin as one of the ingredients shows an effective anti-diabetic activity in a diabetic rat model has been described by Al-Awadi *et al.* (1991).

Antimicrobial Activity

The essential oil produced from the *Boswellia* sp. has proven its effectiveness against several groups of microorganisms such as gram-positive, gram-negative bacterial strains and fungi (Rahimi *et al.,*2010). The experimental study proved that the Acetyl-11-ketobeta-Boswellic acid (AKBA) is the most potential inhibitor of both gam-positive and gram negative bacterial pathogens. The mechanism of action was predicted as the AKBA might be involved in breaking the barrier of lipophilicity of the outer membrane that provides resistance to the pathogens. Similarly, the AKBA was observed to effectively inhibit the biofilm generated by the *Staphylococcus* bacteria, so specifically prevents the growth of *Staphylococcus aureus* and *Staphylococcus epidermidis* (Raja *et al.,* 2011). The essential oil obtained by hydro-distillation mechanism from *B. serrata* has shown its potential antifungal activity against many human pathogens, as well as against plant pathogens (Moleyar & Narasimham, 1986). In an *in-vitro* assay, the *Boswellia* sp. extracts (methanolic and water) has been screened for their potential inhibitory actions against hepatitis C-virus (HCV) by inhibiting the virus protease enzyme (Hussein *et al.,* 2000).

Analgesic and Psychopharmacological Effects

The *B. serrata* plant extracts have shown the analgesic activity in an experimental animal (rat) study in addition to its sedative effect by reducing the spontaneous motor activity (Menon & Kar, 1971). Efficient antidepressant activity of *B. serrata* extracts have been observed in an *acute model of depression*. It was observed that at a dose of 100 mg/kg, *B. serrata* has the notable anti-depressant activity (Al-Harrasi *et al.,* 2019).

Developing Memory

In traditional medicine, *Boswellia* plant product was used to improve the learning and memory in case of pregnant women in order to enhance the memory power as well as the intelligence of the offspring. The significant effects of *B. serrata* extract were studied and subsequently proved its effect to enhance the memory deficits in case of a hypothyroid rat. Since the cell division and activation of central nervous system (CNS) is related to the thyroid hormones, so the deficiency of the hormones cause growth retardation and weak development in specific characters, memory processing, and common intelligence deficits (Hosseini *et al.,* 2010). Therefore, *B. serrata* product was found to significantly improve the memory related problems.

CHALLENGES AND SAFETY ASPECTS OF BOSWELLIC ACID

The extracted gum resin of *B. serrata* has been used as a safe remedy measure for many diseases discussed above without showing any undesirable side effects as described by Siddiqui (2011). Also in comparison to any other drugs, the anti-inflammatory effects of Boswellia products do not cause any kind of remarkable side effects of the body such as heart rate, blood pressure, respiration or any other related responses on the body (Birkner, 2006). Gum resin product of *Boswellia* is enlisted as a safe substance and also sold as anti-inflammatory formulations. The use of this formulated product as a food additive is permitted by United State Food and Drug Administration (USFDA) (Hamidpour *et al.,* 2013). Moreover, the experimental results regarding the side effects of *Boswellia* product is comparatively low as to the modern drug. However, the major limiting factors are low water insolubility and low metabolic stability of AKBA. This limitation can be overcome by using synthetic analogs, combined with other components and using nano scale drug delivery systems. Another challenge is, the standardization of *Boswellia* product is a difficult task as it contains a pool of related product having therapeutically importance. But, the suggested dosages of the boswellia product has been standardized and consists

of 300 - 400 mg of a standardized extract (containing 40-60% boswellic acids) and can be used three times daily for curing of diabetic and osteoarthritic conditions respectively (Ahangarpour *et al.,* 2014). Therefore, the exploration of the *in vivo* mechanism of action of *Boswellia* product is warranted in order to go into the deeper insight of human medication.

CONCLUSION

Boswellic acids, the product of gum resin of *B. serrata* basically consists of a mixture of triterpenic acids. This compound is well known as a therapeutically active molecule and used in the treatment of several diseases including anti-inflammatory, antitumor, immunomodulatory, and other infectious microbial diseases. In the present chapter, the application, and analysis of boswellic acids has been elaborated. Various formulations has been made from such as the extracts by the medium containing petroleum ether, chloroform, and ethanol. The extracts from the bark, leaves, and gum of the plant showed significant clinical efficacy and that is evidenced in many experimental work. In addition to the above, the animals administered with boswellic acid shows no toxicity has been obtained by biochemical haematological, histopathological study. Also, the clinical studies have proven about the good tolerance effect in the treatment of rheumatoid arthritis and Crohn's disease with minimal side effects. Moreover, the *B. serrata* plant possesses a tremendous potential source of therapeutically chemicals deserves for special attention of the scientific community to make this phytomedicine as a milestone for medical science research. Due to its medication profile is concerned, more extensive research on *Boswellia* product and its effect on human medication could lead to exploring the possibility for the novel or alternative natural phytomedicine against harmful diseases and disorders.

REFERENCES

Abdel-Tawab, M., Werz, O., & Schubert-Zsilavecz, M. (2011). Boswellia serrata. *Clinical Pharmacokinetics*, *50*(6), 349–369. doi:10.2165/11586800-000000000-00000 PMID:21553931

Ahangarpour, A., Heidari, H., Fatemeh, R. A. A., Pakmehr, M., Shahbazian, H., Ahmadi, I., & Mhrangiz, B. H. (2014). Effect of Boswellia serrata supplementation on blood lipid, hepatic enzymes and fructosamine levels in type-2 diabetic patients. [PubMed]. *Journal of Diabetes and Metabolic Disorders*, *13*(1), 29. doi:10.1186/2251-6581-13-29

Ahmed, H., Abdel-Rahman, M., Salem, F. E. Z., Shalby, A., & Lokman, M. S. (2014). *Boswellia serrata* and colon cancer: Evidence based approach for treatment. *Planta Medica*, *80*(16), LP20. doi:10.1055-0034-1395080

Al-Awadi, F., Fatania, H., & Shamte, U. (1991). The effect of a plants mixture extract on liver gluconeogenesis in streptozotocin induced diabetic rats. *Diabetes Research (Edinburgh, Scotland)*, *18*(4), 163–168. PMID:1842751

Al-Harrasi, A., Ali, L., Hussain, J., Rehman, N. U., Ahmed, M., & Al-Rawahi, A. (2014). Analgesic effects of crude extracts and fractions of Omani frankincense obtained from traditional medicinal plant *Boswellia sacra* on animal models. *Asian Pacific Journal of Tropical Medicine*, *7*, 485–490. doi:10.1016/S1995-7645(14)60279-0 PMID:25312172

Al-Harrasi, A., Csuk, R., Khan, A., & Hussain, J. (2019). Distribution of the anti-inflammatory and anti-depressant compounds: Incensole and incensole acetate in genus *Boswellia*. *Phytochemistry*, *161*, 28–40. doi:10.1016/j.phytochem.2019.01.007 PMID:30802641

Ammon, H. P. (2002). Boswellic acids (components of frankincense) as the active principle in treatment of chronic inflammatory diseases. *Wiener medizinische Wochenschrift, 152*(15-16), 373-378.

Ammon, H. P. T. (2006). Boswellic acids in chronic inflammatory diseases. *Planta Medica*, *72*(12), 1100–1116. doi:10.1055-2006-947227 PMID:17024588

Ammon, H. P. T. (2010). Modulation of the immune system by *Boswellia serrata* extracts and boswellic acids. *Phytomedicine*, *17*(11), 862–867. doi:10.1016/j.phymed.2010.03.003 PMID:20696559

Ammon, H. P. T., Safayhi, H., Mack, T., & Sabieraj, J. (1993). Mechanism of antiinflammatory actions of curcumine and boswellic acids. *Journal of Ethnopharmacology*, *38*(2-3), 105–112. doi:10.1016/0378-8741(93)90005-P PMID:8510458

Arora, R., Gupta, D., Chawla, R., Sagar, R., Sharma, A., Kumar, R., & Sharma, R. K. (2005). Radioprotection by plant products: Present status and future prospects. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *19*(1), 1–22. doi:10.1002/ptr.1605 PMID:15799007

Banno, N., Akihisa, T., Yasukawa, K., Tokuda, H., Tabata, K., Nakamura, Y., & Suzuki, T. (2006). Anti-inflammatory activities of the triterpene acids from the resin of *Boswellia carteri*. *Journal of Ethnopharmacology*, *107*(2), 249–253. doi:10.1016/j.jep.2006.03.006 PMID:16621377

Birkner, K. M. (2006). Boswellia, the pain herb. *Pain and Stress Publications*, *1*(1), 60–61.

Borrelli, F., Capasso, F., Capasso, R., Ascione, V., Aviello, G., Longo, R., & Izzo, A. A. (2006). Effect of *Boswellia serrata* on intestinal motility in rodents: Inhibition of diarrhea without constipation. *British Journal of Pharmacology*, *148*(4), 553–560. doi:10.1038j.bjp.0706740 PMID:16633355

Cordell, G. A. (2000). Biodiversity and drug discovery -a symbiotic relationship. *Phytochemistry*, *55*(6), 463–480. doi:10.1016/S0031-9422(00)00230-2 PMID:11130658

Ernst, E. (2008). Frankincense: Systematic review. *BMJ (Clinical Research Ed.)*, *337*(dec17 2), 2813. doi:10.1136/bmj.a2813 PMID:19091760

Gerhardt, H., Seifert, F., Buvari, P., Vogelsang, H., & Repges, R. (2001). Therapy of active Crohn's disease with *Boswellia serrata* extract H 15. *Zeitschrift fur Gastroenterologie*, *39*(1), 11–17. doi:10.1055-2001-10708 PMID:11215357

Gerlach, U., & Hiby, W. (1974). Sorbitol dehydrogenase. In *Methods of enzymatic analysis* (pp. 569–573). Academic Press. doi:10.1016/B978-0-12-091302-2.50008-6

Gupta, I., Gupta, V., Parihar, A., Gupta, S., Lüdtke, R., Safayhi, H., & Ammon, H. P. (1998). Effects of *Boswellia serrata* gum resin in patients with bronchial asthma: Results of a double-blind, placebo-controlled, 6-week clinical study. *European Journal of Medical Research*, *3*(11), 511–514. PMID:9810030

Gupta, I., Parihar, A., Malhotra, P., Singh, G. B., Lüdtke, R., Safayhi, H., & Ammon, H. P. (1997). Effects of *Boswellia serrata* gum resin in patients with ulcerative colitis. *European Journal of Medical Research*, *2*(1), 37–43. PMID:9049593

Hamidpour, R., Hamidpour, S., Hamidpour, M., & Shahlari, M. (2013). Frankincense (*Boswellia* species): From the selection of traditional applications to the novel phytotherapy for the prevention and treatment of serious diseases. *Journal of Traditional and Complementary Medicine*, *3*(4), 221. doi:10.4103/2225-4110.119723 PMID:24716181

Hoareau, L., & DaSilva, E. J. (1999). Medicinal plants: A re-emerging health aid. *Electronic Journal of Biotechnology*, *2*(2), 3–4.

Hosseini, M., Hadjzadeh, M. A. R., Derakhshan, M., Havakhah, S., Rassouli, F. B., Rakhshandeh, H., & Saffarzadeh, F. (2010). The beneficial effects of olibanum on memory deficit induced by hypothyroidism in adult rats tested in Morris water maze. *Archives of Pharmacal Research*, *33*(3), 463–468. doi:10.100712272-010-0317-z PMID:20361313

Jing, Y., Nakajo, S., Xia, L., Nakaya, K., Fang, Q., Waxman, S., & Han, R. (1999). Boswellic acid acetate induces differentiation and apoptosis in leukemia cell lines. *Leukemia Research*, *23*(1), 43–50. doi:10.1016/S0145-2126(98)00096-4 PMID:9933134

Kirste, S., Treier, M., Wehrle, S. J., Becker, G., Abdel-Tawab, M., Gerbeth, K., & Momm, F. (2011). *Boswellia serrata* acts on cerebral edema in patients irradiated for brain tumors: A prospective, randomized, placebo-controlled, double-blind pilot trial. *Cancer*, *117*(16), 3788–3795. doi:10.1002/cncr.25945 PMID:21287538

Kirtikar, K. R., & Basu, B. D. (1918). *Indian Medicinal Plants* (vol. 3). Academic Press.

Kumar, D., Kumar, V., & Jalwal, P. (2016). Boswellic Acid-Potential tumors suppressant terpenoid-Photochemistry, Extraction and Isolation Methods-A comprehensive review study. *Journal of Pharmacognosy and Phytochemistry*, *5*(3), 231.

Liu, J. J., & Duan, R. D. (2009). LY294002 enhances boswellic acid-induced apoptosis in colon cancer cells. *Anticancer Research*, *29*(8), 2987–2991. PMID:19661305

Liu, J. J., Nilsson, A., Oredsson, S., Badmaev, V., Zhao, W. Z., & Duan, R. D. (2002). Boswellic acids trigger apoptosis via a pathway dependent on caspase-8 activation but independent on Fas/Fas ligand interaction in colon cancer HT-29 cells. *Carcinogenesis*, *23*(12), 2087–2093. doi:10.1093/carcin/23.12.2087 PMID:12507932

Mannino, G., Occhipinti, A., & Maffei, M. (2016). Quantitative determination of 3-O-acetyl-11-keto-β-boswellic acid (AKBA) and other boswellic acids in *Boswellia sacra* Flueck (syn. B. *carteri Birdw*) and *Boswellia serrata* Roxb. *Molecules (Basel, Switzerland)*, *21*(10), 1329. doi:10.3390/molecules21101329 PMID:27782055

Menon, M. K., & Kar, A. (1971). Analgesic and psychopharmacological effects of the gum resin of *Boswellia serrata. Planta Medica*, *19*(2), 333–341. doi:10.1055-0028-1099651 PMID:5573545

Moleyar, V., & Narasimham, P. (1986). Antifungal activity of some essential oil components. *Food Microbiology*, *3*(4), 331–336. doi:10.1016/0740-0020(86)90017-1

Park, B., Prasad, S., Yadav, V., Sung, B., & Aggarwal, B. B. (2011). Boswellic acid suppresses growth and metastasis of human pancreatic tumors in an orthotopic nude mouse model through modulation of multiple targets. *PLoS One*, *6*(10), e26943. doi:10.1371/journal.pone.0026943 PMID:22066019

Pungle, P., Banavalikar, M., Suthar, A., Biyani, M., & Mengi, S. (2003). Immunomodulatory activity of boswellic acids of *Boswellia serrata* Roxb. *Indian Journal of Experimental Biology*, *14*(12), 460–462. PMID:15320503

Qurishi, Y., Hamid, A., Zargar, M. A., Singh, S. K., & Saxena, A. K. (2010). Potential role of natural molecules in health and disease: Importance of boswellic acid. *Journal of Medicinal Plants Research*, *4*(25), 2778–2786.

Rahimi, R., Shams-Ardekani, M. R., & Abdollahi, M. (2010). A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease. *World Journal of Gastroenterology*, *16*(36), 4504. doi:10.3748/wjg.v16.i36.4504 PMID:20857519

Raja, A. F., Ali, F., Khan, I. A., Shawl, A. S., & Arora, D. S. (2011). Acetyl-11-keto-β-boswellic acid (AKBA); targeting oral cavity pathogens. *BMC Research Notes*, *4*(1), 406. doi:10.1186/1756-0500-4-406 PMID:21992439

Raja, A. F., Ali, F., Khan, I. A., Shawl, A. S., Arora, D. S., Shah, B. A., & Taneja, S. C. (2011). Antistaphylococcal and biofilm inhibitory activities of acetyl-11-keto-β-boswellic acid from *Boswellia serrata. BMC Microbiology*, *11*(1), 54. doi:10.1186/1471-2180-11-54 PMID:21406118

Roy, N. K., Deka, A., Bordoloi, D., Mishra, S., Kumar, A. P., Sethi, G., & Kunnumakkara, A. B. (2016). The potential role of boswellic acids in cancer prevention and treatment. *Cancer Letters*, *377*(1), 74–86. doi:10.1016/j.canlet.2016.04.017 PMID:27091399

Safayhi, H., Mack, T., Sabieraj, J., Anazodo, M. I., Subramanian, L. R., & Ammon, H. P. (1992). Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. *Journal of Pharmacology and Experimental Therapeutics, 261*(3), 1143-1146.

Said, O., Khalil, K., Fulder, S., & Azaizeh, H. (2002). Ethnobotanical survey of medicinal herbs of the Middle Eastern region. *Journal of Ethnopharmacology*, *83*, 251–265. doi:10.1016/S0378-8741(02)00253-2 PMID:12426094

Shao, Y., Ho, C. T., Chin, C. K., Badmaev, V., Ma, W., & Huang, M. T. (1998). Inhibitory activity of boswellic acids from *Boswellia serrata* against human leukemia HL-60 cells in culture. *Planta Medica*, *64*(04), 328–331. doi:10.1055-2006-957444 PMID:9619114

Siddiqui, M. Z. (2011). *Boswellia serrata*, a potential antiinflammatory agent: An overview. *Indian Journal of Pharmaceutical Sciences*, *73*(3), 255. PMID:22457547

Singh, G. B., & Atal, C. K. (1986). Pharmacology of an extract of salaiguggal ex-*Boswellia serrata*, a new non-steroidal anti-inflammatory agent. *Agents and Actions*, *18*(3-4), 407–412. doi:10.1007/BF01965005 PMID:3751752

Singh, S., Khajuria, A., Taneja, S. C., Johri, R. K., Singh, J., & Qazi, G. N. (2008). Boswellic acids: A leukotriene inhibitor also effective through topical application in inflammatory disorders. *Phytomedicine*, *15*(6-7), 400–407. doi:10.1016/j.phymed.2007.11.019 PMID:18222672

Smithson, J., Kellick, K. A., & Mergenhagen, K. (2017). Nutritional modulators of pain in the aging population. In *Nutritional Modulators of Pain in the Aging Population* (pp. 191–198). Academic Press. doi:10.1016/B978-0-12-805186-3.00016-3

Takahashi, M., Sung, B., Shen, Y., Hur, K., Link, A., Boland, C. R., & Goel, A. (2012). Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family. *Carcinogenesis*, *33*(12), 2441–2449. doi:10.1093/carcin/bgs286 PMID:22983985

Wildfeuer, A., Neu, I. S., Safayhi, H., Metzger, G., Wehrmann, M., Vogel, U., & Ammon, H. P. (1998). Effects of boswellic acids extracted from an herbal medicine on the biosynthesis of leukotrienes and the course of experimental autoimmune encephalomyelitis. *Arzneimittel-Forschung*, *48*(6), 668–674. PMID:9689425

Xiufeng, P., Zhengfang, Y., & Zhang, X. (2009). Acetyl-11-Keto-β-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2–mediated angiogenesis. *Cancer Research*, *69*(14), 5893–5900. doi:10.1158/0008-5472.CAN-09-0755 PMID:19567671

Zutshi, U., Rao, P. G., Kaur, S., Singh, G. B., Surjeet, S., & Atal, C. K. (1986). Mechanism of cholesterol lowering effect of Salaiguggal ex. *Boswellia serrata* roxb. *Indian Journal of Pharmacology*, *18*(3), 182.

Chapter 17
Therapeutic Properties of *Syzygium cumini* (Jamun) and *Tinospora cordifolia* (Giloy) Against Various Lethal Diseases

Ankita Gautam
Gautam Buddha University, India

ABSTRACT

Phytochemicals have recently been studied in vivo for their unmatched interactions in curing lethal diseases that can't be cured by allopathic medical intervention without any adverse effect on the patient health. These methods were being used in ancient India, where Jamun and Giloy have been used to decrease hormonal imbalance and pathological disorders. Signaling pathways of the active components of Tinospora cordifolia thus enable effective disease targeting. With so much to offer to the scientific world of medicine, the plant Tinospora truly acts as an incredible source as it deals with seasonal fever like Dengue, Malaria, Chickengunia, and anticancer and anti-HIV (research undergoing). Whereas the Syzygium cumini (Jamun) fruit and seed hold worth in treating various diet-related malfunctions, especially hyperglycemia. In the current research, Jamun seed and fruit extracts have been proved effective in the regulation of blood glucose and insulin parameters.

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INTRODUCTION

In the treatment of traditional diseases, naturopathic doctors prescribe medicines made from natural products like herbs, mixture of herbal components, herbal preparations, and flawless herbal products. The use of natural remedies for treating infections have been widely followed by descendants of most countries throughout the globe. In India the widely followed traditional medicine systems include Unani and Ayurveda. In China, people usually follow and use both traditional medicines and allopathic medicine equally to diagnose, treat and prevent human ailments (Holtz, 2007). The practice of treating diseases by medicines of herbal origin has been increased enormously and two-thirds of the world's population use herbal medicinal products for primary healthcare. Many countries around the world have produced a variety of effective drugs to treat infections and their use all over world is increasing. Some medicinal plants are currently investigated for diuretic and antioxidant actions, and many have been known to have potent diuretic and antioxidant properties. Treatment of the diseases by employing synthetic drugs on one hand give relief to body, but simultaneously they lead to various side effects, and more chances of re-emergence of the disease. Various medicinal plants have been observed to show diuretic and antioxidant assets and researches are continuing to find other plants having these potentials. This chapter highlights the various pharmacological activities of *Syzygium cumini* Linn. Skeels (Myrtaceae) and *Tinospora cordifolia* (Thunb.) Miers (Menispermaceae) and their role in treating different ailments in the human body. Table 1 and 2 described the various pharmacological activities of these plants.

THERAPEUTIC PROPERTIES

Syzgium Cumini Linn. Skeels Myrtaceae) (Syn. Eugenia Jambolana Lam.)

S. cumini is a large evergreen tropical tree and also known as black plum or jambolan. *S. cumini* is very well known for their pharmacological properties. The native home of the *Syzgium* is India and East Indies. The tree fruits once in a year and the berries are sweetish sour to taste. The ripe fruits are used for health drinks, making preserves, squashes, jellies and wine. All parts of the plant especially the seeds are used to treat various diseases, the most important being diabetes mellitus. The medicinal value is due to presence of malic acid (Wealth of India, 2002; Ivan, 2006). Various pharmacological activities of this plant described in table 1.

Gastroprtective and Anti-Ulcerogenic Activities

The gastric mucosal damage was induced in 68 Sprague-Dawley rats by oral gavage administration of HCL/ethanol solution. For investigation, three group were formed, a negative control, an omeprazole group and a tannin group. Microscopic examination using Best's Ulcer Staging Index showed that tannins had a very significant decrease in gastric mucosal damage. Studies for amount of gastric damage also been carried out it shows lower stomach free radical concentration in rats fed with a dose of 20gm tannins/kg of rat (Ramirez & Roa Jr, 2003).

Anti-Inflammatory Activity

The ethanolic bark extract of *S. cumini* has been reported to showed anti-inflammatory activity against histamine, serotonin and prostaglandin. Inflammation was induced by individual autacoids insult, Histamine (1mg/mL), serotonin (5-HT, 1mg/mL), bradykinin (0.02mg/mL) and prostaglandin (PGE2, 0.001mg/mL) was used as inflammogens. The ethanolic extract of this plant showed anti-inflammatory effects in histamine, PGE2 and 5-HT induced rat paw oedema (Pandey & Khan, 2002).

Hypoglycemicand Hypolipidaemic Activity

Defatted seeds and aqueous soluble fibres from seed showed hypoglycaemic activity in alloxan induced diabetic rats. It is showed that *S. cumini* seeds contained 40% of aqueous soluble gummy fibres and 15% of aqueous insoluble fibres. The result of experiment showed that defatted seeds and aqueous soluble gummy fibres from seed significantly lowered the blood glucose level and improved glucose tolerance. Aqueous insoluble fibres do not have significant hypoglycemic activity (Pandey & Khan, 2002; Teixeira *et al.,* 2004). Alcoholic extract of seeds lowered lipid in serum and tissues in alloxan diabetic rats. Hypolipidaemic effect of ethanolic extract was also evident from fall in total serum cholesterol / HDL cholesterol ratio, serum LDL cholesterol level and lowering activity of HMG Co-A reductase. Also histapathological studies of liver, pancreas and aorta in alcoholic extract treated diabetic groups of rabbit revealed almost normal appearance (Sharma *et al.,* 2003).

Antimicrobial Activity

Shaikh *et al.,* (1994) have reported antibacterial activity of ethanolic extracts of *E. jambolana* against gram positive and gram negative bacteria The antibacterial activity of methanol and ethyl acetate extracts of the seeds of *E. jambolana* (at a concentration of 200 µg/disc) against *Bacillus creus, B. subtalis, B. megateriun,*

Steptococcus ß–haemolyticus, *S. aureus*, *Shigella dysenteriae, Sh. Shiga, Sh. boydii, Sh. flexneriae, Sh. sonnei, E. coli, S. typhi B, S. typhi* and *Klebsiella* sp.). Daisy *et al.,* (2007) evaluated on the antibacterial activity of the extract of *S.cumini*. Methanol, acetone and hexane extract of *S.cumini* seeds were examined for antibacterial activity against *Aeromonas hydrophila, Acinetobacter baumannii, Citrobacter freundii, E. coli, Enterobacter aerogenes, K. pneumoniae, P. aeruginosa, Proteus mirabilis.* Methanol extract of *S. cumini* seeds exhibited significant antibacterial activity against tested bacteria. Khan *et al.,* (2016) reported antifungal activity of *S. cumini* bark and leaves extract against *Rhizoctonia solani*. Extracts of bark and leaves of *S. cumini* were prepared in methanol at a concentrations (viz. 1-5%) were tested against the target pathogen. Methanolic bark extract of *S. cumini* was found more effective and showed high antifungal potential as compared to leaf extract. The methanolic bark extract was subjected to bioassay guided fractionation and different organic fractions like ethyl acetate, chloroform, *n*-hexane and *n*-butanol were isolated.

Antioxidant Activity

Ethanolic extract of *S. cumini* seed kernel lowering the increased oxidative stress involved in pathogenesis and progression of diabetic tissue damage. This activity was observed when an increase in levels of plasma glucose, vitamin-E, ceruloplasmin, lipid peroxides and a decrease in levels of vitamin-C and glutathione observed in diabetic rats, recover back to the normal levels after treatment with *S. cumini* seed kernel extract. Histopathological studies also promise its protective activities on pancreatic β-cells (Ravi *et al.,* 2004).

Central Nervous System (CNS) Activity

De Lima *et al.,*(1998) reported different extracts, fractions and sub-fractions from the seeds of *S.cumini* for behavioural effects in mice, particularly in relation to their sedative and anticonvulsant actions. Oral treatment with the hydro-alcoholic extract showed an anticonvulsant activity in pentylenetetrazol and maximal electroshock-induced convulsions, besides a hypothermic effect. The ethyl acetate fraction and its sub-fractions enhanced latency and duration of the first convulsion induced by pentylenetetrazol. *S.cumini* has some active principles with central depressant properties, and some of them also present an anticonvulsant action.

Anti-Allergic Activity

Brito *et al.,*(2007) reported that the *S. cumini* showed anti-allergic activity and indicate that its edematogenic effect is due to the inhibition of mast cell degranulation and of

histamine and serotonin effects whereas the inhibition of eosinophil accumulation in the allergic pleurisy model is probably due to an impairment of CCL11/ eotaxin and IL-5 production.

Gastroprotective Activity

Chaturvedi *et al.,*(2007) reported that the ethanolic extract of seed *E. jambolana* against gastric ulcers induced by 2 h cold restraint stress, pylorus ligation-ethanol and aspirin induced gastric ulcers in rats. The ulcer protective activity of *E. jambolana* may be due to its effects on both offensive and defensive factors. The antioxidant properties of *E. jambolana* contribute towards its activity.

Antifertility Activity

Rajasekaran *et al.,*(1998) has reported anti-fertility activity of oleanolic acid isolated from the flowers of *E. jambolana* significant decreased the fertilizing capacity of the male albino rats without any important change in body or reproductive organ weights. It causes significant reduction in conversion of spermatocytes to spermatides and arrest of spermatogenesis at the early stages of meiosis leading to decrease in sperm count without any aberration to spermatogenic cells, leyding interstitial cells and sertoli cells.

Anti-Diarrhoeal Activity

Mukherjee *et al.,*(1998) reported the anti-diarrhoeal activity of ethanol extract of *S. cumini* against different experimental models of diarrhoea in rats. It produced significant inhibition of castor oil induced diarrhoea and PGE- induced entero-pooling and a significant reduction in gastrointestinal motility in charcoal meal tests in rats. Shamkuwar *et al.,* (2012) evaluated anti-diarrhoeal, antimotility and anti-secretory activity of aqueous seed extract *S. cumini* in castor oil induced diarrhoea method.

Antipyretic Activity

Chaudhuri *et al.,* (1990) reported that the chloroform extracts of dried seeds showed antipyretic activity. Mahapatra *et al.,* (1986) reported methanol extracts of dried seeds administered intra-peritoneal to rats at doses of 50 mg per kg were active versus yeast induced pyrexia.

Antispasmodic Activity

Dhawan *et al.,* (1977) reported that the ethanol-water (1:1) extract of the aerial parts were inactive in guinea pig ileum vs. acetyl choline and histamine induced spasms. The ethanol water (1:1) of dried bark of a concentration of 0.01 g/mL, was found active on guinea pig ileum.

Antiviral Activity

Rana *et al.,* (1992) evaluated the ethanol and water (1:1) extract of dried whole plant, at a concentration of 0.1 mg/ml in cell culture, was inactive on Ranikhet virus and vaccinia virus. For Ranikhet virus, infected chorioallantoic membrane viral titre decreased 10% and for vaccinia virus 0%.

Cardio-Protective Activity

The hydro-alcoholic extract of *S. cumini* was evaluated for its antihypertensive, and vaso-relaxant effect. Polyethylene catheters were inserted into the inferior vena cava and lower abdominal aorta in the anaesthetized rats for dosing and measuring blood pressure. The extract at the doses of 0.5; 1; 5; 10; 20 and 30 mg/kg, i.v. was able to induce hypotension (due to reduction in endothelium mediated peripheral resistance) and bradycardia (Herculano *et al.,* 2014).

Antinociceptive Activity

The hydro-alcoholic leaf extract of *S. cumini* was evaluated for its analgesic potential in rats. To assess the cutaneous nociception, hot plate and formalin tests were used while for muscular nociception, forelimb grip force was measured. The extract at the dose of 100–300 mg/kg i.p. exhibited a significant decrease in the pain scores in all the phases of the formalin test but extract even at the dose of 300 mg/kg was not able to modify the grip force in intact rats (Avila-Peña *et al.,* 2007).

Anticancer and Chemoprotective Activity

Afify *et al.,* (2011) evaluated the anticancer activity of *S. cumini* fruits extracts using cell viability assay of leukaemia cancer cell line. They prepared extracts of hexane, chloroform, ether, ethyl acetate, ethanol, and water and evaluated anticancer activity. They reported that the ethanol extract exhibited stronger anti-leukaemia activity as compared to other ones. Spectroscopic findings of active ingredients separated from ethanol extract showed that fruit extract of *S. cumini* contained phenolic compounds

Table 1. Different pharmacological activities of S. cumini

Sr. No.	Pharmacological Activity	Part/s used	Phytochemical/ crude extract	References
1.	Anti-hyperlipidemic activity	Seed	Ethanolic extract	Ravi *et al.,* (2005)
2.	Anti-hyperlipidemic activity	Pulp	Aqueous extract	Rekha *et al.,* (2008)
3.	Antioxidant activity, free radical scavenging and anti-lipid peroxidative activity	Seed	Aqueous extract	Ravi *et al.,* (2004); Prince *et al.,* (2003); Ahmed *et al.,* (2010)
4.	Antioxidant activity	Leaf	Methanolic extract	Ruan *et al.,* (2008)
5.	Anti-ulcer activity	Seed	Ethanolic extract	Chaturvedi *et al.,* (2007)
6.	Hepatoprotective activity	Pulp	Ethanolic extract	Das & Sarme, (2009)
7.	Anti-allergic activity	Leaf	Aqueous extract	Brito *et al.,*(2007)
8.	Anti-arthritic activity	Seed	Methanolic extract	Kumar *et al.,* (2008)
9.	Antibacterial activity	Bark	Aqueous and acetone extract	Djipa *et al.,* (2000)
10.	Radioprotective activity	Seed	Hydro-alcoholic extract	Abalea *et al.,* (1999)
11.	Central nervous system (CNS) activity	Seed	Ethyl acetate and methanolic extract	Kumar *et al.,* (2007)
12.	Anti-diarrhoeal effect	Bark	Ethanolic extract	Tripathi, (1994)
13.	Nephroprotective activity	Pulp	FIIc, isolated from aqueous Extract	Tanwar *et al.,* (2010)
14.	Anti-inflammatory effect	Seed	Ethyl acetate and methanolic extract	Kumar *et al.,* (2008)

namely kaempferol 7-O-methylether and sterols such as γ-sitosterol was responsible for their anticancer activity. Various herbal drugs have proved their beneficial effect in protecting healthy tissues from the toxic effects of anticancer drugs. The aqueous and ethanolic *S. cumini* seed extracts have shown chemo-protective action in the *in vivo* oxidative stress and genomic damage (Arun *et al.,* 2011).

Tinospora Cordifolia (Thunb.) Miers (Menispermaceae)

T. cordifolia commonly called as Guduchi is a natural herbal shrub. This plant is useful in treatment of several diseases like jaundice, skin diseases, gout, diabetes etc. which has been established in the history of traditional medicine practices. In

this perspective, *T. cordifolia* is considered to be a nectar plant and has been called as amrita in Sanskrit in recognition of its detoxifying, rejuvenating, and immune boosting properties. In modern medicine, the herb has been evaluated and studied more profoundly and most recently the drug is implemented to mitigate the negative effects of chemotherapy (Preeti, 2011). Various pharmacological activities of this plant described in table 2.

THERAPEUTIC ACTIVITIES

Hypoglycemic Activity

Oral administration of the water extract of *T.cordifolia* root caused a significant reduction in blood glucose, brain lipid level, hepatic glucose-6-phosphatase, serum acid phosphatase, alkaline and lactate dehydrogenase and increase in body weight, total haemoglobin and hepatic hexokinase in alloxanized diabetic rats (Stanely *et al.,* 2000).

Anti-Allergic Activity

In a clinical study, 100% relief was reported from sneezing in 83% of the patients on treatment with *T. cordifolia*. Thus *T. cordifolia* significantly decreased all symptoms of allergic rhinitis and was well tolerated (Badar *et al.,* 2005).

Cardioprotective Activity

A dose-dependent reduction in infarct size and in serum and heart lipid peroxide levels was observed with prior treatment with *T. cordifolia* in ischemia-reperfusion-induced myocardial infarction in rats (Rao *et al.,*2005).

Hepatoprotective Activity

The hepatoprotective action of *T. cordifolia* was reported in one of the experiment in which goats treated with *T. cordifolia* have shown significant clinical and hemato-biochemical improvement in CCl4 induced hepatopathy. Extract of *T. cordifolia* has also exhibited *in vitro* inactivating property against hepatitis B and E surface antigen in 48-72 H (Mehrotra *et al.,* 2000).

Anti-Stress and Tonic Property

The anti-stress and tonic property of the plant was clinically tested and it was found that it brought about good response in children with moderate degree of behaviour disorders and mental deficit. It has also significantly improved the I.Q. levels (Singh *et al.,* 2003).

Antineoplastic Activity

Intraperitoneal injection of the alcoholic extract of *T. cordifolia* has been shown to Dalton's lymphoma (DL) bearing mice stimulated macrophage functions like phagocytosis, antigen-presenting ability and secretion of Interleukin-1 (IL-1), tumour necrosis factor (TNF) and Reference Nutrient Intake (RNI) as well as slowed tumour growth and increased lifespan of the tumour-bearing host (Singh *et al.,* 2005).

Osteoprotective Activity

Rats treated with *T. cordifolia* showed an osteoprotective effect, as the bone loss in tibiae was slower than that in controls. Serum osteocalcin and cross-laps levels were significantly reduced. This study demonstrates that extract of *T. cordifolia* has the potential for being used as antiosteoporotic agent (Kapur *et al.,* 2008).

Antifertility Activity

Oral administration of 70% methanolic extract of *T. cordifolia* stem to male rats at a dose level of 100 mg/d for 60 days did not cause body weight loss but decreased the weight of testes, epididymis, seminal vesicle and ventral prostate in a significant manner (Gupta & Sharma, 2003).

Antiulcer Activity

Treatment with a formulation containing *T. cordifolia* has been shown to reduce ulcer index total acidity, with an increase in the pH of gastric fluid in pylorus-ligated rats and in the ethanol-induced gastric mucosal injury in rats (Bafna & Balaraman, 2005).

Antileprotic Activity

T. cordifolia is used for its kushtahara (anti-leprotic) properties, along with wide use in Kandu and visarpa (types of skin disorders) and has been shown to exert antileprotic activity in a combination formulation (Asthana *et al.,* 2001).

Anticancer Activity

Various experimental models of animal have been taken to show the anticancer activity of plant *T. cordifolia*. The cultured HeLa cells when exposed to different concentration of methylene chloride extracts of *T. cordifolia* such as 5, 10, 25, 50, and 100 μg/ml. It showed an increase in cell death or cell killing as compared to untreated cultured cell (control) in a dose-dependent manner (Jagetia *et al.,* 1998). A study has also reported that, the hydro-alcoholic extract of roots (aerial) of *T. cordifolia* on exposure to the liver as well as extra-hepatic organs of mice (at 50 and 100mg/kg body weight) shows an increase in glutathione (GSH) level and other metabolizing enzymes. In addition to this, there is a significant decrease in production of malonaldehyde (MLD) level representing a decrease in free radical formation providing an antioxidative state of cell (Singh *et al.,* 2006).

Antioxidant Activity

T. cordifolia have a potential ability to scavenge free radical and shows a protective effect by altering different hormone and mineral levels. *T. cordifolia* has reported to reverse the toxicity caused by aflatoxin in kidney (Swiss albino mice) where, it substantially elevates the hormone level (such as glutathione) and enzyme activities (such as catalase, glutathione reductase); and decreases the reactive oxygen species (ROS) and this anti-toxin activity is primarily brought by the alkaloids of this plant (Gupta & Sharma, 2011).

Antidiabetic Activity

The compounds such as alkaloids, cardiac glycosides, saponins, flavonoids, tannins and steroids isolated from *T. cordifolia* possess antidiabetic property. Hence, it makes possible to have wide application in clinical as well as experimental study. Alkaloids from *T. cordifolia* stated to possess the effect like insulin hormone and shows insulin mediated actions (Patel & Mishra, 2011). Gestational diabetes can increase the GSH content and other reactive species that can act as a threat to the mother as well as foetus. However, a study stated that when *T. cordifolia* has been given in daily diet to a diabetic-pregnant rat (streptozocin induced diabetes), it shows a protective effect by reducing the oxidative load thereby preventing the relative incidence of diseases and any sort of birth defect (Shivananjappa, 2012).

Immunomodulatory Activity

Isolated chemical compounds such as cordifolioside A and syringin of *T. cordifolia* are reported as immunomodulating agent in the clinical study (Sharma *et al.,* 2012). *T. cordifolia* stem alters the level of enzymes such as catalase and stimulates lymphocyte cells maintaining the immune strength, thus highlighting the immuno-protective role of this shrub (Aher & Wahi, 2012). Macrophage cell when exposed to *T. cordifolia* extract, increases the production of different enzymes including 'myeloperoxidase' that enhances the anti-microbial action so as to protect the immunity (More & Pai, 2012).

Anti-HIV Activity

T. cordifolia has been evaluated to found its importance in treating HIV positive patients by decreasing the patient's resistance to the retroviral regimen (Gupta *et al.,* 2010). The anti-HIV activity of *T. cordifolia* uncovers its application in managing the disease by increasing the CD4 T-cells count and decreasing eosinophil-(a type of WBC) count in HIV positive patients. *T. cordifolia* extract showed significantly enhanced phagocytic and intracellular bactericidal activity. *T. cordifolia* also stimulated peritoneal macrophage (Patel *et al.,* 2013; Kalikar *et al.,* 2008).

Antimicrobial Activity

A study reported that silver nanoparticles synthesized from the stem of *T. cordifolia* possess good antibacterial activity against the bacteria *Pseudomonas aeruginosa* found in the patient suffering from burn injury (Singh *et al.,* 2014). Various bacterial strains such as *S. typhi, K. pneumoniae, E.coli, P. aeruginosa* and other bacteria have been tested against extracts of *T. cordifolia* and showed potential anti-bacterial activity by either inhibiting their growth or mitigating the very existence of these bacteria (Narayanan *et al.,* 2011; Tambekar *et al.,* 2009). A hydro alcoholic extract of *T. cordifolia* was effective in the mammary inflammation induced in bovine model by enhancing the activity of granulocyte. As mastitis is due to the infection of *S. aureus,* prevention of this inflammation showed the antimicrobial activity of this plant (Mukherjee *et al.,* 2010; Purandare & Supe, 2007).

Anti-Osteoporotic Activity

An *in vitro* study suggested, that the alcoholic extract of *T. cordifolia* was found to enhance the degree of proliferation and differentiation of the osteoblast cells of both human and rats. Over and above it also take part in the calcification process

Table 2. Pharmacological activities of Tinospora cordifolia (Thunb.) Miers

Sr. No.	Pharmacological Activity	Part/s used	Phytochemical/ extract	References
1.	Cardioprotective activity	Whole plant	Alcohol extract	Gupta & Sharma, (2011)
2.	Antiulcer activity	Whole plant	Ethanol and / aqueous extracts	Mishra & Kaur (2015)
3.	Antidiarrheal activity	Whole plant	Ethanol and aqueous extract	Mishra & Kaur (2013)
4.	Immunomodulatory activity	Whole plant	Aqueous extract	Sengupta *et al.,* (2011)
5.	Neuroprotective effect	Aerial parts	Ethanol extract	Kosaraju *et al.,* (2014)
6.	Anti-inflammatory activity	Stem	Aqueous extract	Patgiri *et al.,* (2014)
7.	Gastroprotective activity	Whole plant	Ethanol extract	Antonisamy *et al.,* (2014)
8.	Antioxidant activity	Whole plant		Jayaprakash *et al.,* (2015)
9.	Radio protective and Cytoprotective activity	Stem	Ethanol extract	Patel *et al.,* (2013)
10.	Antifeedant activity	Whole plant	Chloroform extract	Sivasubramanian *et al.,* (2013)
11.	Ameliorative activity	Root	Ethanol extract	Gupta & Sharma, (2011)
12.	Hepatoprotective activity	Whole plant	Aqueous extract	Stanca *et al.,* (2011)
13.	Nootropic activity	Whole plant	Ethanol extract	Gupta *et al.,* (2013)
14.	Hypoglycemic activity	Stem	Aqueous extract	Patel & Mishra, (2011)
15.	Antiosteoporotic activity	Stem	Ethanol extract	Kapur *et al.,* (2008)
16.	Antineoplastic activity	Aerial parts	Dichloromethane extract	Jagetia & Rao, (2006)
17.	Antifertility effect	Stem	Methanol extract	Gupta & Sharma, (2003)
18.	Antiasthamatic activity	Stem	Hydro-alcoholic Extract	Tiwari *et al.,* (2014)
19.	Diabetic neuropathy	Stem	aqueous extract	Nadig *et al.,* (2012)
20.	Antimalarial activity	Stem	Ethanolic extract	Dhanasekaran *et al.,* (2009)
21.	Hepatocellular carcinoma	Aerial parts	Ether extract	Dhanasekaran *et al.,* (2009)
22.	Antibacterial activity	Stem	Aqueous and ethanolic extract	Jeyachandran *et al.,* (2003)

by producing minerals by these bone forming cell models regulating the bone mineralization (Abiramasundari *et al.,* 2012). A steroid named 'Beta- Ecdysone' or 20-hydroxyecdysone isolated from *T. cordifolia* showed to promote the building of muscle tissue in mesenchymal stem cells model of mouse preventing the incidence of osteoporosis (Gao *et al.,* 2008; Kapur *et al.,* 2010).

CONCLUSION

S. cumini commonly known as 'jamun' also having various pharmacological activities such as anti-diarrhoeal, astringent, digestive, antibacterial, antioxidant, antiviral but most important activity is antidiabetic. Although most of the studies of *S. cumini* as anti-diabetic agent with its possible mechanism of action and delaying complications of diabetes such as cataract, neuropathy have been conducted but detailed research on isolation of bioactives through clinical trials followed by standardisation is seriously required to know potential of the plant.

T. cordifolia is a natural herbal shrub and very useful in treatment of several diseases like jaundice, skin diseases, gout, diabetes etc. which has been established in the history of traditional medicine practices. In this perspective, *T. cordifolia* is considered to be a nectar plant and has been called as amrita in Sanskrit in recognition of its detoxifying, rejuvenating, and immune boosting properties. In modern medicine, the herb has been evaluated and studied more profoundly and most recently the drug is implemented to mitigate the negative effects of chemotherapy. Most of the pharmacological work was carried out on seeds and other parts of *T. cordifolia* and *S. cumini* but the pharmacological potential of other parts also required to be explored.

REFERENCES

Abalea, V., Cillard, J., Dubos, M. P., Sergent, O., Cillard, P., & Morel, I. (1999). Repair of iron induced DNA oxidation by the flavonoid myericetin in primary rat hepatocyte culture. *Free Radical Biology & Medicine*, *26*(11-12), 1457–1466. doi:10.1016/S0891-5849(99)00010-6 PMID:10401609

Abiramasundari, G., Sumalatha, K. R., & Sreepriya, M. (2012). Effects of *Tinospora cordifolia* (Menispermaceae) on the proliferation, osteogenic differentiation and mineralization of osteoblast model systems *in vitro*. *Journal of Ethnopharmacology*, *141*(1), 474–480. doi:10.1016/j.jep.2012.03.015 PMID:22449439

Afify, A. E., Fayed, S. A., Shalaby, E. A., & El-Shemy, H. A. (2011). *Syzygium cumini* (pomposia) active principles exhibit potent anticancer and antioxidant activities. *African Journal of Pharmacy and Pharmacology*, *5*(7), 948–956.

Aher, V., & Wahi, A. K. (2012). Biotechnological approach to evaluate the immunomodulatory activity of ethanolic extract of *Tinospora cordifolia* stem (mango plant climber). *Iranian Journal of Pharmaceutical Research*, *11*(3), 863–872. PMID:24250513

Ahmed, F., Huded, S., & Malik, F. A. (2010). *In vitro* study on the radical scavenging and anti lipidperoxidative effects of *Eugenia jambolana* aqueous extracts. *Journal of Pharmacy Research*, *3*(1), 198–200.

Antonisamy, P., Dhanasekaran, M., Ignacimuthu, S., Duraipandiyan, V., Balthazar, J. D., Agastian, P., & Kim, J.-H. (2014). Gastroprotective effect of epoxy clerodane diterpene isolated from *Tinospora cordifolia* Miers (Guduchi) on indomethacin-induced gastric ulcer in rats. *Phytomedicine*, *21*(7), 966–969. doi:10.1016/j.phymed.2014.02.010 PMID:24680619

Arun, R., Prakash, M. V., Abraham, S. K., & Premkumar, K. (2011). Role of *Syzygium cumini* seed extract in the chemoprevention of in vivo genomic damage and oxidative stress. *Journal of Ethnopharmacology*, *134*(2), 329–333. doi:10.1016/j.jep.2010.12.014 PMID:21182920

Asthana, Jain, & Ashutosh, & VijayKanth. (2001). Evaluation of antileprosy herbal drug combinations and their combinations with dapsone. *Indian Drugs*, *38*, 82–86.

Avila-Peña, D., Peña, N., Quintero, L., & Suárez-Roca, H. (2007). Antinociceptive activity of *Syzygium jambos* leaves extract on rats. *Journal of Ethnopharmacology*, *112*(2), 380–385. doi:10.1016/j.jep.2007.03.027 PMID:17478066

Badar, V. A., Thawani, V. R., Wakode, P. T., Shrivastava, M. P., Gharpure, K. J., Hingorani, L. L., & Khiyani, R. M. (2005). Efficacy of *Tinospora cordifolia* in allergic rhinitis. *Journal of Ethnopharmacology*, *96*(3), 445–449. doi:10.1016/j.jep.2004.09.034 PMID:15619563

Bafna, P. A., & Balaraman, R. (2005). Anti-ulcer and antioxidant activity of pepticare, a herbomineral formulation. *Phytomedicine*, *12*(4), 264–270. doi:10.1016/j.phymed.2003.12.009 PMID:15898703

Brito, F. A., Lima, L. A., Ramos, M. F., Nakamura, M. J., Cavalher-Machado, S. C., Siani, A. C., ... Sampaio, A. L. (2007). Pharmacological study of anti-allergic activity of *Syzygium cumini* (L.) Skeels. *Brazilian Journal of Medical and Biological Research*, *40*(1), 105–115. doi:10.1590/S0100-879X2007000100014 PMID:17225003

Castillo, A. L., Ramos, J. D., De Francia, J. L., Quilala, P. F., & Dujunco, M. U. (2014). Immunomodu latory effects of *Tinospora cordifolia* lotion on interleukin-1, interleukin-6 and interleukin-8 levels in scabies-infected paediatric patients: A single blind, randomized trial. *International Journal of Pharmaceutical Sciences and Drug Research*, *6*(3), 204–210.

Chaturvedi, A., Kumar, M. M., Bhawani, G., Chaturvedi, H., Kumar, M., & Goel, R. K. (2007). Effect of ethanolic extract of *Eugenia jambolana* seeds on gastric ulceration and secretion in rats. *Indian Journal of Physiology and Pharmacology*, *51*(2), 131–141. PMID:18175656

Chaudhuri, A. K., Pal, S., Gomes, A., & Bhattacharya, S. (1990). Anti-inflammatory and related actions of *Syzygium cuminii* seed extract. *Phytotherapy Research*, *4*(1), 5–10. doi:10.1002/ptr.2650040103

Daisy, P. (2007). *A process for preparation of a novel compound 5,6-dihydroxy-3-[(4-hydroxy-6- (hydroxymethyl)-3,5-di[3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2h-2pyranyl} oxytrtahydro-2h-2pranyl)oxy]2methoxy10,13dimethylper hycyclopenta[aphenanthren-17-yl [phenyl]methyl acetate from Syzygium cumini (L.) skeels seeds with antibacterial and antidiabetic activity*. Patent Application No.810/CHE/2007.

Das, S., & Sarme, G. (2009). Study of the hepatoprotective activity of the ethanolic extract of the pulp of *Eugenia jambolana* (Jamun) in albino rats. *Journal of Clinical and Diagnostic Research: JCDR*, *3*, 1466–1474.

De Lima, T. C., Klüeger, P. A., Pereira, P. A., Macedo-Neto, W. P., Morato, G. S., & Farias, M. R. (1998). Behavioural effects of crude and semi-purified extracts of *Syzygium cuminii* Linn. Skeels. *Phytotherapy Research*, *12*(7), 488–493. doi:10.1002/(SICI)1099-1573(199811)12:7<488::AID-PTR344>3.0.CO;2-0

Dhanasekaran, M., Baskar, A. A., Ignacimuthu, S., Agastian, P., & Duraipandiyan, V. (2009). Chemopreventive potential of Epoxy clerodane diterpene from *Tinospora cordifolia* against diethyl nitrosamine-induced hepatocellular carcinoma. *Investigational New Drugs*, *27*(4), 347–355. doi:10.100710637-008-9181-9 PMID:18853103

Dhawan, B. N., Patnaik, G. K., Rastogi, R. P., Singh, K. K., & Tandon, J. S. (1977). Screening of Indian plants for biological activity: Part VI. *Indian Journal of Experimental Biology*, *15*(3), 208–219. PMID:914326

Djipa, C. D., Delmee, M., & Quetin-Leclercq, J. (2000). Antimicrobial activity of bark extracts of *Syzygium jambos* (L.) Alston (Myrtaceae). *Journal of Ethnopharmacology*, *71*(1-2), 307–313. doi:10.1016/S0378-8741(99)00186-5 PMID:10904178

Gao, L., Cai, G., & Shi, X. (2008). β-Ecdysterone induces osteogenic differentiation in mouse mesenchymal stem cells and relieves osteoporosis. *Biological & Pharmaceutical Bulletin*, *31*(12), 2245–2249. doi:10.1248/bpb.31.2245 PMID:19043207

Gupta, A., Karchuli, M., & Upmanyu, N. (2013). Comparative evaluation of ethanolic extracts of Bacopa monnieri, Evolvulus alsinoides, *Tinospora cordifolia* and their combinations on cognitive functions in rats. *Current Aging Science*, *6*(3), 239–243. doi:10.2174/18746098112059990036 PMID:23866011

Gupta, G. D., Sujatha, N., Dhanik, A., & Rai, N. P. (2010). Clinical evaluation of Shilajatu Rasayana in patients with HIV infection. *Ayurveda*, *31*(1), 28–32. doi:10.4103/0974-8520.68205 PMID:22131681

Gupta, R., & Sharma, V. (2011). Ameliorative effects of *Tinospora cordifolia* root extract on histopathological and biochemical changes induced by aflatoxin-B1 in mice kidney. *Toxicology International*, *18*(2), 94. doi:10.4103/0971-6580.84259 PMID:21976812

Gupta, R. S., & Sharma, A. (2003). Antifertility effect of *Tinospora cordifolia* (Willd.) stem extract in male rats. *Indian Journal of Experimental Biology*, *41*, 885–889. PMID:15248490

Herculano, E. D., da Costa, C., Rodriques, A. K., Araújo-Júnior, J. X., Santana, E. G., França, P. H., ... Ribeiro, Ê. A. (2014). Evaluation of cardiovascular effects of edible fruits of *Syzygium cumini* Myrtaceae (L) Skeels in rats. *Tropical Journal of Pharmaceutical Research*, *13*(11), 1853–1861. doi:10.4314/tjpr.v13i11.12

Holtz, C. (2007). *Global Health Care: Issues and Policies*. Sudbury, MA: Jones & Barlett Publishers.

Ivan, A. R. (2006). *Medicinal Plant of World: Chemical Constituents*. Traditional Uses and Modern Medicinal Uses, Human Press Totowa.

Jabeen, K., & Javaid, A. (2010). Antifungal activity of *Syzygium cumini* against *Ascochyta rabiei*–the cause of chickpea blight. *Natural Product Research*, *24*(12), 1158–1167. doi:10.1080/14786410902941154 PMID:19588279

Jagetia, G. C., Nayak, V., & Vidyasagar, M. S. (1998). Evaluation of the antineoplastic activity of guduchi (*Tinospora cordifolia*) in cultured HeLa cells. *Cancer Letters*, *127*(1), 71–82. doi:10.1016/S0304-3835(98)00047-0 PMID:9619860

Jagetia, G. C., & Rao, S. K. (2006). Evaluation of the antineoplastic activity of guduchi (*Tinospora cordifolia*) in Ehrlich ascites carcinoma bearing mice. *Biological & Pharmaceutical Bulletin*, *29*(3), 460–466. doi:10.1248/bpb.29.460 PMID:16508146

Jayaprakash, R., Ramesh, V., Sridhar, M. P., & Sasikala, C. (2015). Antioxidant activity of ethanolic extract of *Tinospora cordifolia* on N-nitrosodiethylamine (diethyl nitrosamine) induced liver cancer in male Wister albino rats. *Journal of Pharmacy & Bioallied Sciences*, *7*(5S1), 40. doi:10.4103/0975-7406.155791 PMID:26015745

Jeyachandran, R., Xavier, T. F., & Anand, S. P. (2003). Antibacterial activity of stem extracts of *Tinospora cordifolia* (Willd) Hook. F and Thomson. *Ancient Science of Life*, *23*(1), 40–43. PMID:22557111

Kalikar, M. V., Thawani, V. R., Varadpande, U. K., Sontakke, S. D., Singh, R. P., & Khiyani, R. K. (2008). Immunomodulatory effect of *Tinospora cordifolia* extract in human immuno-deficiency virus positive patients. *Indian Journal of Pharmacology*, *40*(3), 107–110. doi:10.4103/0253-7613.42302 PMID:20040936

Kapur, P., Jarry, H., Wuttke, W., Pereira, B. M., & Seidlova-Wuttke, D. (2008). Evaluation of the antiosteoporotic potential of *Tinospora cordifolia* in female rats. *Maturitas*, *59*(4), 329–338. doi:10.1016/j.maturitas.2008.03.006 PMID:18482809

Kapur, P., Wuttke, W., Jarry, H., & Seidlova-Wuttke, D. (2010). Beneficial effects of β-Ecdysone on the joint, epiphyseal cartilage tissue and trabecular bone in ovariectomized rats. *Phytomedicine*, *17*(5), 350–355. doi:10.1016/j.phymed.2010.01.005 PMID:20171072

Khan, A., Jabeen, K., & Iqbal, S. (2016). Antifungal activity of *Syzygium cumini* L. against Rhizoctoniasolani. *Pure and Applied Biology*, *5*(2), 193–199. doi:10.19045/bspab.2016.50025

Kirtikar, K. R., & Basu, B. D. (1933). Indian Medicinal Plants (vol. 2). Lalit Mohan Basu.

Kosaraju, J., Chinni, S., Roy, P. D., Kannan, E., Antony, A. S., & Kumar, M. S. (2014). Neuro-protective effect of *Tinospora cordifolia* ethanol extract on 6-hydroxy dopamine induced Parkinsonism. *Indian Journal of Pharmacology*, *46*(2), 176–180. doi:10.4103/0253-7613.129312 PMID:24741189

Kumar, A., Ilavarasan, R., Jayachandran, T., Deecaraman, M., Kumar, R. M., & Aravindan, P. (2008). Anti-inflammatory activity of *Syzygium cumini* seed. *African Journal of Biotechnology*, *7*(8), 941–943.

Kumar, A., Padmanabhan, N., & Krishana, M. R. V. (2007). Central nervous system activity of *Syzigium cumini* seeds. *Pakistan Journal of Nutrition*, *6*(6), 698–700. doi:10.3923/pjn.2007.698.700

Kumar, A., Padmanabhan, N., & Krishnan, M. R. (2007). Central nervous system activity of *Syzygium cumini* seed. *Pakistan Journal of Nutrition*, *6*(6), 698–700. doi:10.3923/pjn.2007.698.700

Kumar, E. K., Mastan, S. K., Reddy, K. R., Reddy, G. A., Raghunandan, N., & Chaitanya, G. (2008). Antiarthritic property of methanolic extract of *Syzygium cumini* seeds. *International Journal of Integrative Biology*, *4*, 55.

Mahapatra, P. K., Chakraborty, D., & Chaudhuri, A. N. (1986). Anti-inflammatory and antipyretic activities of *Syzygium cuminii. Planta Medica*, *52*(6), 540. doi:10.1055-2007-969339 PMID:17345495

Mehrotra, R., Katiyar, C. K., & Gupta, A. P. (2000). *Hepatoprotective composition and composition for treatment of conditions related to hepatitis band E infection*. US Patent, 6, 136, 316.

Mishra, R., & Kaur, G. (2013). Aqueous ethanolic extract of *Tinospora cordifolia* as a potential candidate for differentiation-based therapy of glioblastomas. *PLoS One*, *8*(10), e78764. doi:10.1371/journal.pone.0078764 PMID:24205314

Mishra, R., & Kaur, G. (2015). *Tinospora cordifolia* induces differentiation and senescence pathways in neuroblastoma cells. *Molecular Neurobiology*, *52*(1), 719–733. doi:10.100712035-014-8892-5 PMID:25280667

Mokkhasmit, M., Swasdimongkol, K., Ngarmwathana, W., Stanley, M. P. P., Kamalakkannan, N., & Menon, V. P. (2003).. . *Journal of Ethnopharmacology*, *84*(2-3), 205–209. doi:10.1016/S0378-8741(02)00316-1 PMID:12648817

More, P., & Pai, K. (2012). *In vitro* NADH-oxidase, NADPH-oxidase and myeloperoxidase activity of macrophages after *Tinospora cordifolia* (guduchi) treatment. *Immunopharmacology and Immunotoxicology*, *34*(3), 368–372. doi:10.3109/08923973.2011.606324 PMID:22295977

Mukherjee, P. K., Saha, K., Murugesan, T., Mandal, S. C., Pal, M., & Saha, B. P. (1998). Screening of anti-diarrhoeal profile of some plant extracts of a specific region of West Bengal, India. *Journal of Ethnopharmacology*, *60*(1), 85–89. doi:10.1016/S0378-8741(97)00130-X PMID:9533436

Mukherjee, R., De, U. K., & Ram, G. C. (2010). Evaluation of mammary gland immunity and therapeutic potential of *Tinospora cordifolia* against bovine subclinical mastitis. *Tropical Animal Health and Production*, *42*(4), 645–651. doi:10.100711250-009-9471-z PMID:19876755

Nadig, P. D., Revankar, R. R., Dethe, S. M., Narayanswamy, S. B., & Aliyar, M. A. (2012). Effect of *Tinospora cordifolia* on experimental diabetic neuropathy. *Indian Journal of Pharmacology*, *44*(5), 580–583. doi:10.4103/0253-7613.100380 PMID:23112417

Narayanan, A., Raja, S., Ponmurugan, K., Kandekar, S., Natarajaseenivasan, K., Maripandi, A., & Mandeel, Q. (2011). Antibacterial activity of selected medicinal plants against multiple antibiotic resistant uropathogens: A study from Kolli Hills, Tamil Nadu, India. *Beneficial Microbes*, *2*(3), 235–243. doi:10.3920/BM2010.0033 PMID:21986363

Pandey, M., & Khan, A. (2002). Hypoglycaemic effect of defatted seeds and water soluble fibre from the seeds of *Syzygium cumini* (Linn.) skeels in alloxan diabetic rats. *Indian Journal of Experimental Biology*, *40*(10), 1178–1182. PMID:12693701

Patel, A., Bigoniya, P., Singh, C. S., & Patel, N. S. (2013). Radioprotective and cytoprotective activity of *Tinospora cordifolia* stem enriched extract containing cordifolioside-A. *Indian Journal of Pharmacology*, *45*(3), 237–243. doi:10.4103/0253-7613.111919 PMID:23833365

Patel, M. B., & Mishra, S. (2011). Hypoglycemic activity of alkaloidal fraction of *Tinospora cordifolia. Phytomedicine*, *18*(12), 1045–1052. doi:10.1016/j.phymed.2011.05.006 PMID:21665451

Patgiri, B., Umretia, B. L., Vaishnav, P. U., Prajapati, P. K., Shukla, V. J., & Ravishankar, B. (2014). Anti-inflammatory activity of guduchi ghana (aqueous extract of *Tinospora cordifolia* Miers.). *Ayu*, *35*(1), 108–110. doi:10.4103/0974-8520.141958 PMID:25364210

Preeti, S. (2011). *Tinospora cordifolia* (Amrita)-a miracle herb and lifeline too many diseases. *International Journal of Medicinal and Aromatic Plants*, *1*(2), 57–61.

Prince, P.S., Menon, V.P., & Pari, L. (1998). Hypoglycaemic activity of *Syzigium cumini* seeds: effect on lipid peroxidation in alloxan diabetic rats. *Journal of Ethnopharmacology, 61*(1), 1-7.

Prince, P. S. M., Kamalakkannan, N., & Menon, V. P. (2003). *Syzigium cumini* seed extracts reduce tissue damage in diabetic rat brain. *Journal of Ethnopharmacology*, *84*(2-3), 205–209. doi:10.1016/S0378-8741(02)00316-1 PMID:12648817

Purandare, H., & Supe, A. (2007). Immunomodulatory role of *Tinospora cordifolia* as an adjuvant in surgical treatment of diabetic foot ulcers: A prospective randomized controlled study. *Indian Journal of Medical Sciences*, *61*(6), 347–355. doi:10.4103/0019-5359.32682 PMID:17558098

Rajasekaran, M., Bapna, J. S., Lakshmanan, S., Nair, A. R., Veliath, A. J., & Panchanadam, M. (1988). Antifertility effect in male rats of oleanolic acid, a triterpene from *Eugenia jambolana* flowers. *Journal of Ethnopharmacology*, *24*(1), 115–121. doi:10.1016/0378-8741(88)90142-0 PMID:3199836

Ramirez, R.O., & Roa Jr, C.C. (2003). The gastroprotective effect of tannins extracted from duhat (*Syzygium cumini* Skeels) bark on HCl/ethanol induced gastric mucosal injury in Sprague-Dawley rats. *Clinical Hemorheology and Microcirculation, 29*(3-4), 253-261.

Rana, N. S., & Joshi, M. N. (1992). Investigation on the antiviral activity of ethanolic extracts of *Sysygium* sp. *Fitoterapia*, *63*, 542–544.

Rao, P. R., Kumar, V. K., Viswanath, R. K., & Subbaraju, G. V. (2005). Cardioprotective activity of alcoholic extract of *Tinospora cordifolia* in ischemia-reperfusion induced myocardial infarction in rats. *Biological & Pharmaceutical Bulletin*, *28*(12), 2319–2322. doi:10.1248/bpb.28.2319 PMID:16327173

Ravi, K., Rajasekara, S., & Subramanian, S. (2005). Anti-hyperlipidemic effect of *Eugenia jambolana* seed kernel on streptozotocin-induced diabetes in rats. *Food and Chemical Toxicology*, *43*(9), 1433–1439. doi:10.1016/j.fct.2005.04.004 PMID:15964674

Ravi, K., Ramachandran, B., & Subramanian, S. (2004). Effect of *Eugenia jambolana* seed kernel on antioxidant defense system in streptozotocin-induced diabetes in rats. *Life Sciences*, *75*(22), 2717–2731. doi:10.1016/j.lfs.2004.08.005 PMID:15369706

Rekha, N., Balaji, R., & Deecaraman, M. (2008). Effect of aqueous extract of *Syzygium cumini* pulp on anti-oxidant defense system in streptozotocin induced diabetic rats. *Ir. J Pharmacol Ther*, *7*, 137–145.

Ruan, Z. P., Zhang, L. L., & Lin, Y. M. (2008). Evaluation of the antioxidant activity of S*yzygium cumini* leaves. *Molecules (Basel, Switzerland)*, *13*(10), 2545–2556. doi:10.3390/molecules13102545 PMID:18927517

Sengupta, M., Sharma, G. D., & Chakraborty, B. (2011). Effect of aqueous extract of *Tinospora cordifolia* on functions of peritoneal macrophages isolated from CCl4 intoxicated male albino mice. *BMC Complementary and Alternative Medicine*, *11*(1), 102. doi:10.1186/1472-6882-11-102 PMID:22035196

Shaikh, R. M., Baqir, M. F., Naqvi, S., & Shaikh, D. (1994). Partial purification and antibacterial studies of extracts from *Eugenia jambolana* Linn and *Vincarosea* Linn. *Pakistan Journal of Scientific and Industrial Research*, *37*, 279–281.

Shamkuwar, P. B., Pawar, D. P., & Chauhan, S. S. (2012). Antidiarrhoeal activity of seeds of *Syzygium cumini* L. *Journal of Pharmacy Research*, *5*(12).

Sharma, S.B., Nasir, A., Prabhu, K.M., Murthy, P.S., & Dev, G. (2003). Hypoglycaemic and hypolipidemic effect of ethanolic extract of seeds of *Eugenia jambolana* in alloxan-induced diabetic rabbits. *Journal of Ethnopharmacology, 85*(2), 201-206.

Sharma, U., Bala, M., Kumar, N., Singh, B., Munshi, R. K., & Bhalerao, S. (2012). Immuno modulatory active compounds from *Tinospora cordifolia. Journal of Ethnopharmacology*, *141*(3), 918–926. doi:10.1016/j.jep.2012.03.027 PMID:22472109

Sharma, V., & Pandey, D. (2010). Beneficial effects of *Tinosporacordifolia*on blood profiles in male mice exposed to lead. *Toxicology International*, *17*(1), 8. doi:10.4103/0971-6580.68341 PMID:21042466

Shivananjappa, M. M., & Muralidhara. (2012). Abrogation of maternal and fetal oxidative stress in the streptozotocin-induced diabetic rat by dietary supplements of *Tinospora cordifolia. Nutrition (Burbank, Los Angeles County, Calif.)*, *28*(5), 581–587. doi:10.1016/j.nut.2011.09.015 PMID:22189193

Singh, K., Panghal, M., Kadyan, S., Chaudhary, U., & Yadav, J. P. (2014). Antibacterial activity of synthesized silver nanoparticles from *Tinospora cordifolia* against multi drug resistant strains of *Pseudomonas aeruginosa* isolated from burn patients. *Journal of Nanomedicine & Nanotechnology*, *5*(2), 1–6. doi:10.4172/2157-7439.1000192

Singh, N., Singh, S. M., & Shrivastava, P. (2005). Immunomodulatory and antitumor actions of medicinal plant *Tinospora cordifolia* are mediated through activation of tumor-associated macrophages. *Immunopharmacology and Immunotoxicology*, *26*(1), 145–162. doi:10.1081/IPH-120029952 PMID:15106739

Singh, R. P., Banerjee, S., Kumar, P. V., Raveesha, K. A., & Rao, A. R. (2006). *Tinospora cordifolia* induces enzymes of carcinogen/drug metabolism and antioxidant system and inhibits lipid peroxidation in mice. *Phytochemistry*, *13*(1-2), 74–84. PMID:16360936

Singh, S. S., Pandey, S. C., Srivastava, S., Gupta, V. S., Patro, B., & Ghosh, A. C. (2003). Chemistry and medicinal properties of *Tinospora cordifolia. Indian Journal of Pharmacology*, *35*, 83–91.

Sivasubramanian, A., Gadepalli, N. K. K., Rathnasamy, R., & Campos, A. M. (2013). A new antifeedant clerodane diterpenoid from *Tinospora cordifolia*. *Natural Product Research*, *27*(16), 1431–1436. doi:10.1080/14786419.2012.722088 PMID:22946632

Stanca, M.H., Nagy, A., Tosa, M. & Vlad, L. (2011). Hepatoprotective effects of orally administered melatonin and *Tinospora cordifolia* in experimental jaundice. *Chirurgia, 106*(2), 205-210.

Stanely, P., Prince, M., & Menon, V. P. (2000). Hypoglycemic and other related actions of *Tinospora cordifolia* roots in alloxan-induced diabetic rats. *Journal of Ethnopharmacology*, *70*(1), 9–15. doi:10.1016/S0378-8741(99)00136-1 PMID:10720784

Tambekar, D. H., Khante, B. S., Chandak, B. R., Titare, A. S., Boralkar, S. S., & Aghadte, S. N. (2009). Screening of antibacterial potentials of some medicinal plants from Melghat forest in India. *African Journal of Traditional, Complementary, and Alternative Medicines*, *6*, 228–232. PMID:20448847

Tanwar, R. S., Sharma, S. B., Singh, U. R., & Prabhu, K. M. (2010). Attenuation of renal dysfunction by anti-hyperglycemic compound isolated from fruit pulp of *Eugenia jambolana* in streptozotocin induced diabetic rats. *Indian Journal of Biochemistry & Biophysics*, *47*, 83–89. PMID:20521620

Teixeira, C. C., Weinert, L. S., Barbosa, D. C., Ricken, C., Esteves, J. F., & Fuchs, F. D. (2004). *Syzygium cumini* (L.) Skeels in the treatment of type 2 diabetes. *Diabetes Care*, *27*(12), 3019–3020. doi:10.2337/diacare.27.12.3019-a PMID:15562231

Tiwari, M., Dwivedi, U. N., & Kakkar, P. (2014). *Tinospora cordifolia* extract modulates COX-2, iNOS, ICAM-1, pro-inflammatory cytokines and redox status in murine model of asthma. *Journal of Ethnopharmacology*, *153*(2), 326–337. doi:10.1016/j.jep.2014.01.031 PMID:24556222

Tripathi, K. D. (1994). Essentials of Medical Pharmacology. Jaypee Brothers, Medical Publishers (P).

Wealth of India. (2002). A Dictionary of Indian Raw materials and Industrial Products, National Institute of Science Communication, Council of Scientific and Industrial Research. New Delhi. *Raw Materials*, *10*, 100–107.

Compilation of References

Abalea, V., Cillard, J., Dubos, M. P., Sergent, O., Cillard, P., & Morel, I. (1999). Repair of iron induced DNA oxidation by the flavonoid myericetin in primary rat hepatocyte culture. *Free Radical Biology & Medicine*, *26*(11-12), 1457–1466. doi:10.1016/S0891-5849(99)00010-6 PMID:10401609

Abbasi, A. M., Khan, M. A., Ahmed, M., & Zafar, M. (2010). Herbal medicines used to cure various ailments by the inhabitants of Abbottabad district, North West Frontier Province, Pakistan. *Indian Journal of Traditional Knowledge*, *9*, 175–183.

Abd El-Hafeez, A. A., Khalifa, H. O., Mahdy, E. A. M., Sharma, V., Hosoi, T., Ghosh, P., ... Kawamoto, S. (2019). Anticancer effect of nor-wogonin (5, 7, 8-trihydroxyflavone) on human triple-negative breast cancer cells via down regulation of TAK1, NF-κB, and STAT3. *Pharmacological Reports*, *71*(2), 289–298. doi:10.1016/j.pharep.2019.01.001 PMID:30826569

Abdel-Tawab, M., Werz, O., & Schubert-Zsilavecz, M. (2011). Boswellia serrata. *Clinical Pharmacokinetics*, *50*(6), 349–369. doi:10.2165/11586800-000000000-00000 PMID:21553931

Abdullahi, A. A. (2011). Trends and challenges of traditional medicine in Africa. *African Journal of Traditional, Complementary, and Alternative Medicines*, *8*(5S), 115–123. doi:10.4314/ajtcam.v8i5S.5 PMID:22754064

Abiramasundari, G., Sumalatha, K. R., & Sreepriya, M. (2012). Effects of *Tinospora cordifolia* (Menispermaceae) on the proliferation, osteogenic differentiation and mineralization of osteoblast model systems *in vitro*. *Journal of Ethnopharmacology*, *141*(1), 474–480. doi:10.1016/j.jep.2012.03.015 PMID:22449439

Abolaji, A. O., Adebayo, A. H., & Odesanmi, O. S. (2007). Effects of *Parinari polyandra* (Rosaceae) on serum lipid profile and some electrolytes in pregnant rabbits. *Research Journal of Medicinal Plant*, *1*(4), 121–127. doi:10.3923/rjmp.2007.121.127

Achan, J., Talisuna, A. O., Erhart, A., Yeka, A., Tibenderana, J. K., Baliraine, F. N., ... D'Alessandro, U. (2011). Quinine, an old anti-malarial drug in amodern world: Role in the treatment of malaria. *Malaria Journal*, *10*(1), 144. doi:10.1186/1475-2875-10-144 PMID:21609473

Adeneye, A. A., & Agbaje, E. O. (2007). Hypoglycemic and hypolipidemic effects of fresh leaf aqueous extract of *Cymbopogon citratus* Stapf. in rats. *Journal of Ethnopharmacology*, *112*(3), 440–444. doi:10.1016/j.jep.2007.03.034 PMID:17513076

Adeyemi, D. O., Komolafe, O. A., Adewole, S. O., & Obuotor, E. M. (2009). Anti-hyperlipidemic activities of *Annona muricata* (Linn). *The Internet Journal of Alternative Medicine*, *7*(1), 1–9.

Adhirajan, N., Kumar, T. R., Shanmugasundaram, N., & Babu, M. (2003). *In vivo* and *in vitro* evaluation of hair growth potential of *Hibiscus rosa-sinensis* Linn. *Journal of Ethnopharmacology*, *88*(2-3), 235–239. doi:10.1016/S0378-8741(03)00231-9 PMID:12963149

Afandi, A., Zulkiffli, H., Sadikun, A., & Ismail, S. (2014). Antioxidant properties of *Gynura procumbens* extracts and their inhibitory effects on two major human recombinant cytochrome P450S using a high throughput luminescence assay. *Asian Journal of Pharmaceutical and Clinical Research*, *7*(5), 36–41.

Afify, A. E., Fayed, S. A., Shalaby, E. A., & El-Shemy, H. A. (2011). *Syzygium cumini* (pomposia) active principles exhibit potent anticancer and antioxidant activities. *African Journal of Pharmacy and Pharmacology*, *5*(7), 948–956.

Agarwal, A., Malini, S., Bairy, K. L., & Rao, M. S. (2002). Effect of *Tinospora cardifolia* on learning and memory in normal and memory deficit rats. *Indian Journal of Pharmacology*, *34*(5), 339–349.

Agarwal, O. P. (1985). Prevention of atheromatous heart disease. *Angiology*, *36*(8), 485–492. doi:10.1177/000331978503600801 PMID:2864002

Aggarwal, B. B., Surh, Y. J., & Shishodia, S. (Eds.). (2007). *The molecular targets and therapeutic uses of curcumin in health and disease* (Vol. 595). Springer Science & Business Media. doi:10.1007/978-0-387-46401-5_1

Ahangarpour, A., Heidari, H., Fatemeh, R. A. A., Pakmehr, M., Shahbazian, H., Ahmadi, I., & Mhrangiz, B. H. (2014). Effect of Boswellia serrata supplementation on blood lipid, hepatic enzymes and fructosamine levels in type-2 diabetic patients. [PubMed]. *Journal of Diabetes and Metabolic Disorders*, *13*(1), 29. doi:10.1186/2251-6581-13-29

Aher, V., & Wahi, A. K. (2012). Biotechnological approach to evaluate the immunomodulatory activity of ethanolic extract of *Tinospora cordifolia* stem (mango plant climber). *Iranian Journal of Pharmaceutical Research*, *11*(3), 863–872. PMID:24250513

Ahmad, A., Senapati, S., Khan, M. I., Kumar, R., Ramani, R., Srinivas, V., & Sastry, M. (2003). Intrecellular synthesis of gold nanoparticles by a novel alkalotolerant actinomycete Rhodococcus species. *Nanotechnology*, *14*(7), 824–825. doi:10.1088/0957-4484/14/7/323

Ahmadi, B. B., Bahmani, M., Eftekhari, Z., Jelodari, M., & Mirhoseini, M. (2016). Overview of medicinal plants used for cardiovascular system disorders and diseases in ethnobotany of different areas in Iran. *Journal of Herbmed Pharmacology*, *5*, 39–44.

Ahmed, F., Chandra, J., & Res, A. U.J. P., & U. (2009). In vitro antioxidant and anticholinesterase activity of *Acorus calamus* and *Nardostachys jatamansi* rhizomes. *Journal of Pharmacy Research*, *2*(5), 830–833.

Ahmed, F., Huded, S., & Malik, F. A. (2010). *In vitro* study on the radical scavenging and anti lipidperoxidative effects of *Eugenia jambolana* aqueous extracts. *Journal of Pharmacy Research*, *3*(1), 198–200.

Ahmed, H., Abdel-Rahman, M., Salem, F. E. Z., Shalby, A., & Lokman, M. S. (2014). *Boswellia serrata* and colon cancer: Evidence based approach for treatment. *Planta Medica*, *80*(16), LP20. doi:10.1055-0034-1395080

Ahmed, Q. U., Sarian, M. N., Mat So'ad, S. Z., Latip, J., Arief Ichwan, S., Hussein, N., ... Fakurazi, S. (2018, November 15). Methylation and Acetylation Enhanced the Antidiabetic Activity of Some Selected Flavonoids: *In vitro*, Molecular Modelling and Structure Activity Relationship-Based Study. *Biomolecules*, *8*(4), 149. doi:10.3390/biom8040149

Ahrazem, O., Gómez-Gómez, L., Rodrigo, M. J., Avalos, J., & Limón, M. C. (2016). Carotenoid cleavage oxygenases from microbes and photosynthetic organisms: Features and functions. *International Journal of Molecular Sciences*.

Akbar, Y., Kumaraswamy, R., & Shanmugam, R. (2014). Optimization and stabilization of gold nanoparticles by using herbal plant extract with microwave heating. *Nano Convergence*, *1*(1), 12–18. doi:10.118640580-014-0012-8 PMID:28191395

Akinloye, O. A., & Solanke, O. O. (2011). Evaluation of hypolipidemic and potential antioxidant effects of *Pigeon pea* (*Cajanus cajan* (l) mill sp.) leaves in alloxan-induced hyperglycemic rats. *Journal of Medicinal Plants Research*, *5*, 2521–2524.

Akpan, E. J., Okokon, J. E., & Offong, E. (2012). Antidiabetic and hypolipidemic activities of ethanolic leaf extract and fractions of *Melanthera scandens. Asian Pacific Journal of Tropical Biomedicine*, *2*(7), 523–527. doi:10.1016/S2221-1691(12)60089-6 PMID:23569963

Alam, A. (2012). Some Indian bryophytes known for their biologically active compounds. *International Journal of Applied Biology and Pharmaceutical Technology*, *3*(2), 239–246.

Alam, F., & Us Saqib, Q. N. (2017). Evaluation of *Zanthoxylum armatum* Roxb for *in vitro* biological activities. *Journal of Traditional and Complementary Medicine*, *7*(4), 515–518. doi:10.1016/j.jtcme.2017.01.006 PMID:29034201

Al-Awadi, F., Fatania, H., & Shamte, U. (1991). The effect of a plants mixture extract on liver gluconeogenesis in streptozotocin induced diabetic rats. *Diabetes Research (Edinburgh, Scotland)*, *18*(4), 163–168. PMID:1842751

Aldred, K. J., Kerns, R. J., & Osheroff, N. (2014). Mechanism of quinolone action and resistance. *Biochemistry*, *53*(10), 1565–1574. doi:10.1021/bi5000564 PMID:24576155

Alemdar, S., & Agaoglu, S. (2009). Investigation of *in vitro* antimicrobial activity of *aloe vera* juice. *Journal of Animal and Veterinary Advances*, *8*, 99–102.

Al-Harrasi, A., Ali, L., Hussain, J., Rehman, N. U., Ahmed, M., & Al-Rawahi, A. (2014). Analgesic effects of crude extracts and fractions of Omani frankincense obtained from traditional medicinal plant *Boswellia sacra* on animal models. *Asian Pacific Journal of Tropical Medicine*, *7*, 485–490. doi:10.1016/S1995-7645(14)60279-0 PMID:25312172

Al-Harrasi, A., Csuk, R., Khan, A., & Hussain, J. (2019). Distribution of the anti-inflammatory and anti-depressant compounds: Incensole and incensole acetate in genus *Boswellia. Phytochemistry*, *161*, 28–40. doi:10.1016/j.phytochem.2019.01.007 PMID:30802641

Alifrangis, M., Nag, S., Schousboe, M. L., Ishengoma, D., Lusingu, J., Pota, H., ... Cox, J. (2014). Independent origin of *Plasmodium falciparum* antifolate super-resistance, Uganda, Tanzania, and Ethiopia. *Emerging Infectious Diseases*, *20*(8), 1280–1286. doi:10.3201/eid2008.131897 PMID:25061906

Ali, H., Houghton, P. J., & Soumyanath, A. (2006). α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to *Phyllanthus amarus. Journal of Ethnopharmacology*, *107*(3), 449–455. doi:10.1016/j.jep.2006.04.004 PMID:16678367

Ali, H., & Qaiser, M. (2009). The ethnobotany of Chitral valley, Pakistan with particular reference to medicinal plants. *Pakistan Journal of Botany*, *41*, 2009–2041.

Alscher, R. G., Donahue, J. L., & Cramer, C. L. (1997). Reactive oxygen species and antioxidants: Relationships in green cells. *Physiologia Plantarum*, *100*(2), 224–233. doi:10.1111/j.1399-3054.1997.tb04778.x

Al-Sereiti, M. R., Abu-Amer, K. M., & Sena, P. (1999). *Pharmacology of rosemary (*Rosmarinus officinalis *Linn.) and its therapeutic potentials*. Academic Press.

Al-Snafi, A. E. (2018). Chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa-sinensis* -A review. *Journal of Pharmaceutics*, *8*(7), 101–119.

Alves, R. R., & Rosa, I. M. (2007). Biodiversity, traditional medicine and public health: Where do they meet? *Journal of Ethnobiology and Ethnomedicine*, *3*(1), 3. doi:10.1186/1746-4269-3-14 PMID:17376227

Alwi, I., Santoso, T., Suyono, S., Sutrisna, B., Suyatna, F. D., Kresno, S. B., & Ernie, S. (2008). The effect of curcumin on lipid level in patients with acute coronary syndrome. *Acta Medica Indonesiana*, *40*(4), 201–210. PMID:19151449

Amakura, Y., Yoshimura, M., Sugimoto, N., Yamazaki, T., & Yoshida, T. (2009). Marker constituents of the natural antioxidant *Eucalyptus* leaf extract for the evaluation of food additives. *Bioscience, Biotechnology, and Biochemistry*, *73*(5), 1060–1065. doi:10.1271/bbb.80832 PMID:19420705

Amin, B., & Hosseinzadeh, H. (2016). Black cumin (*Nigella sativa*) and its active constituent, thymoquinone: an overview on the analgesic and anti-inflammatory effects. *Planta medica*, *82*(1/2), 816.

Ammon, H. P. (2002). Boswellic acids (components of frankincense) as the active principle in treatment of chronic inflammatory diseases. *Wiener medizinische Wochenschrift, 152*(15-16), 373-378.

Ammon, H. P. T. (2006). Boswellic acids in chronic inflammatory diseases. *Planta Medica*, *72*(12), 1100–1116. doi:10.1055-2006-947227 PMID:17024588

Ammon, H. P. T. (2010). Modulation of the immune system by *Boswellia serrata* extracts and boswellic acids. *Phytomedicine*, *17*(11), 862–867. doi:10.1016/j.phymed.2010.03.003 PMID:20696559

Ammon, H. P. T., Safayhi, H., Mack, T., & Sabieraj, J. (1993). Mechanism of antiinflammatory actions of curcumine and boswellic acids. *Journal of Ethnopharmacology*, *38*(2-3), 105–112. doi:10.1016/0378-8741(93)90005-P PMID:8510458

Amrita, M., Suraj, K. T., & Soon-Il, Y. (2012). Fungus mediated synthesis of gold nanoparticles and their conjugation with genomic DNA isolated from *Escherichia coli* and *Staphylococcus aureus. Process Biochemistry*, *47*(5), 701–711. doi:10.1016/j.procbio.2012.01.017

Ande, K.K., Gowrishankar, N.L., Manju Bhargavi, V., Nagarjuna, M., Rajani, G., Swetha, Y., & Vinay Reddy, P. (2012). Evaluation of antiulcer activity of ethanol extract of *Diospyros melanoxylon* (Roxb) Bark. *Int. J. Pharm. & Pharmaceu. Sc, 4*(4), 537-539.

Andersen, O. M., & Markham, K. R. (2005). Flavonoids: Chemistry, Biochemistry and Applications. CRC Press. doi:10.1201/9781420039443

Anderson, J. W., Davidson, M. H., Blonde, L., Brown, W. V., Howard, W. J., Ginsberg, H., & Weingand, K. W. (2000). Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *The American Journal of Clinical Nutrition*, *71*(6), 1433–1438. doi:10.1093/ajcn/71.6.1433 PMID:10837282

Andrade-Cetto, A., & Wiedenfeld, H. (2004). Hypoglycemic effect of *Acosmium panamense* bark on streptozotocin diabetic rats. *Journal of Ethnopharmacology*, *90*(2-3), 217–220. doi:10.1016/j.jep.2003.09.049 PMID:15013183

Andreolas, C., da Silva Xavier, G., Diraison, F., Zhao, C., Varadi, A., Lopez-Casillas, F., & Rutter, G. A. (2002). Stimulation of acetyl-CoA carboxylase gene expression by glucose requires insulin release and sterol regulatory element binding protein 1c in pancreatic MIN6 β-cells. *Diabetes*, *51*(8), 2536–2545. doi:10.2337/diabetes.51.8.2536 PMID:12145168

Anekonda, T. S., & Reddy, P. H. (2005). Can herbs provide a new generation of drugs for treating Alzheimer's disease? *Brain Research. Brain Research Reviews*, *50*(2), 361–376. doi:10.1016/j.brainresrev.2005.09.001 PMID:16263176

Angahar, L. T. (2017). An overview of breast cancer epidemiology, risk factors, pathophysiology, and cancer risks reduction. *MOJ Biol Med*, *1*(4), 92–96. doi:10.15406/mojbm.2017.01.00019

Ani, V., Varadaraj, M. C., & Naidu, K. A. (2006). Antioxidant and antibacterial activities of polyphenolic compounds from bitter cumin (*Cuminum nigrum* L.). *European Food Research and Technology*, *224*(1), 109–115. doi:10.100700217-006-0295-z

Annamalai, A., Christina, V. L. P., Sudha, D., Kalpana, M., & Lakshmi, P. T. V. (2013). Green synthesis characterization and antimicrobial activity of AuNPs using Euphobia hitra L. leaf extract. *Colloids and Surfaces. B, Biointerfaces*, *108*, 60–65. doi:10.1016/j.colsurfb.2013.02.012 PMID:23528605

Anonymous. (1989). The Ayurvedic Pharmacopoeia of India. Ministry of Health and Family Welfare, Department of Health, Govt. of India.

Anonymous. (2005). *The Wealth of India-Raw Materials*. New Delhi: Council of Scientific and Industrial Research.

Ansari, N., & Khodagholi, F. (2013). Natural products as promising drug candidates for the treatment of Alzheimer's disease: Molecular mechanism aspect. *Current Neuropharmacology*, *11*(4), 414–429. doi:10.2174/1570159X11311040005 PMID:24381531

Ansari, N., Khodagholi, F., & Amini, M. (2011). 2-Ethoxy-4, 5-diphenyl-1, 3-oxazine-6-one activates the Nrf2/HO-1 axis and protects against oxidative stress-induced neuronal death. *European Journal of Pharmacology*, *658*(2-3), 84–90. doi:10.1016/j.ejphar.2011.02.028 PMID:21371450

Antonisamy, P., Dhanasekaran, M., Ignacimuthu, S., Duraipandiyan, V., Balthazar, J. D., Agastian, P., & Kim, J.-H. (2014). Gastroprotective effect of epoxy clerodane diterpene isolated from *Tinospora cordifolia* Miers (Guduchi) on indomethacin-induced gastric ulcer in rats. *Phytomedicine*, *21*(7), 966–969. doi:10.1016/j.phymed.2014.02.010 PMID:24680619

Apel, K., & Hirt, H. (2004). Reactive oxygen species: Metabolism, oxidative stress, and signal transduction. *Annual Review of Plant Biology*, *55*(1), 373–399. doi:10.1146/annurev.arplant.55.031903.141701 PMID:15377225

Apostolidis, E., Kwon, Y. I., & Shetty, K. (2007). Inhibitory potential of herb, fruit, and fungal-enriched cheese against key enzymes linked to type 2 diabetes and hypertension. *Innovative Food Science & Emerging Technologies*, *8*(1), 46–54. doi:10.1016/j.ifset.2006.06.001

Aqil, F., & Ahmad, I. Z. M. T. U. (2006). Antioxidant and free radical scavenging properties of twelve traditionally used Indian medicinal plants. *Turkish Journal of Biology*, *30*(3), 177–183.

Arafa, H. M. (2005). Curcumin attenuates diet-induced hypercholesterolemia in rats. *Medical Science Monitor*, *11*(7), BR228–BR234. PMID:15990684

Arakawa, T. (1962). Effect of Swertinogen on hair growth with special reference to its activities on skin function. *The Tokushima Journal of Experimental Medicine*, *9*, 37–59. PMID:14013531

Archana, N. P., & Anita, A. M. (2006). A study on clinical efficacy of *Lepidium sativum* seeds in treatment of bronchial asthma. *Iranian Journal of Pharmacology and Therapeutics*, *5*, 55–59.

Arora, R., Gupta, D., Chawla, R., Sagar, R., Sharma, A., Kumar, R., & Sharma, R. K. (2005). Radioprotection by plant products: Present status and future prospects. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *19*(1), 1–22. doi:10.1002/ptr.1605 PMID:15799007

Arulmozhi, S., Rasal, V. P., Sathiyanarayanan, L., & Purnima, A. (2007). *Screening of* Alstonia scholaris *Linn. R. Br., for wound healing activity*. Academic Press.

Arumugam, P., Priya, N. G., Subathra, M., & Ramesh, A. (2008). Anti-inflammatory activity of four solvent fractions of ethanol extract of *Mentha spicata* L. investigated on acute and chronic inflammation induced rats. *Environmental Toxicology and Pharmacology*, *26*(1), 92–95. doi:10.1016/j.etap.2008.02.008 PMID:21783894

Arunachalam, K. D., & Annamalai, S. K. (2013). Chrysopogon zizanioides aqueous extract mediated synthesis characterization of crystalline silver and gold nanoparticles for biomedical applications. *International Journal of Nanomedicine*, *8*, 2375–2384. doi:10.2147/IJN.S44076 PMID:23861583

Arunachalam, K. D., Annamalai, S. K., & Hari, S. (2013). One-step green synthesis and characterization of leaf extracts-mediated biocompatible silver and gold nanoparticles from Memocylon umbellatus. *International Journal of Nanomedicine*, *8*, 307–315.

Arunkumar, S., & Muthuselvam, M. (2009). Analysis of phytochemical constituents and antimicrobial activities of *Aloe vera* L. against clinical pathogens. *World Journal of Agricultural Sciences*, *5*(5), 572–576.

Arun, R., Prakash, M. V., Abraham, S. K., & Premkumar, K. (2011). Role of *Syzygium cumini* seed extract in the chemoprevention of in vivo genomic damage and oxidative stress. *Journal of Ethnopharmacology*, *134*(2), 329–333. doi:10.1016/j.jep.2010.12.014 PMID:21182920

Aruoma, O. I. (1994). Nutrition and health aspects of free radicals and antioxidants. *Food and Chemical Toxicology*, *32*(7), 671–683. doi:10.1016/0278-6915(94)90011-6 PMID:8045480

Asada, K., & Takahashi, M. (1987). Production and scavenging of active oxygen in chloroplasts. In *Photoinhibition* (pp. 227–287). Photoinhibition.

Asakawa, Y. (1981). Biologically active substances obtained from bryophytes. *The Journal of the Hattori Botanical Laboratory*, (50): 123–142.

Asakawa, Y. (2007). Biologically active compounds from bryophytes. *Pure and Applied Chemistry*, *79*(4), 557–580. doi:10.1351/pac200779040557

Asakawa, Y., Toyota, M., Taira, Z., & Takemoto, T. (1982). Biologically active cyclic bisbenzyls and terpenoids isolated from liverworts. *Proceeding of the 25th Symposium on Chemistry of Natural Products*, 337-344.

Ashabi, G., Ramin, M., Azizi, P., Taslimi, Z., Alamdary, S. Z., Haghparast, A., & Khodagholi, F. (2012). ERK and p38 inhibitors attenuate memory deficits and increase CREB phosphorylation and PGC-1α levels in Aβ-injected rats. *Behavioural Brain Research*, *232*(1), 165–173. doi:10.1016/j.bbr.2012.04.006 PMID:22510382

Ashraf, R., Khan, R. A., & Ashraf, I. (2011). Garlic (*Allium sativum*) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. *Pakistan Journal of Pharmaceutical Sciences*, *24*(4), 565–570. PMID:21959822

Asthana, Jain, & Ashutosh, & VijayKanth. (2001). Evaluation of antileprosy herbal drug combinations and their combinations with dapsone. *Indian Drugs*, *38*, 82–86.

Auddy, B., Ferreira, M., Blasina, F., Lafon, L., Arredondo, F., Dajas, F., & Mukherjee, B. (2003). Screening of antioxidant activity of three Indian medicinal plants, traditionally used for the management of neurodegenerative diseases. *Journal of Ethnopharmacology*, *84*(2-3), 131–138. doi:10.1016/S0378-8741(02)00322-7 PMID:12648805

Avello, M., Jofre, P., Pastene, E., & Fernandez, P. (2014). Use of *Citrus limon* L. (lemon) in treating blood pressure sudden rises. *International Journal of Pharmacognosy and Phytochemical Research*, *6*(3), 606–611.

Avila-Peña, D., Peña, N., Quintero, L., & Suárez-Roca, H. (2007). Antinociceptive activity of *Syzygium jambos* leaves extract on rats. *Journal of Ethnopharmacology*, *112*(2), 380–385. doi:10.1016/j.jep.2007.03.027 PMID:17478066

Ayati, Z., Ramezani, M., Amiri, M. S., Moghadam, A. T., Rahimi, H., Abdollahzade, A., & Sahebkar, A. (2019). Ethnobotany, phytochemistry and traditional uses of *Curcuma* spp. and pharmacological profile of two important species (*C. longa* and *C. zedoaria*): a review. *Current Pharmaceutical Design.*

Azuelo, A. G., Sariana, L. G., & Pabulan, M. P. (2011). Some medicinal bryophytes: Their Ethnomedical Uses and Morphology. *Asian Journal of Biodiversity*, *2*(1), 49–80. doi:10.7828/ajob.v2i1.92

Azu, N. C., Onyeagba, R. A., Nworie, O., & Kalu, J. (2007). Antibacterial activity of *Allium cepa* (Onions) and *Zingiber officinale* (Ginger) on *Staphylococcus aureus* and *Pseudomonas aeruginosa* isolated from high vaginal swab. *Internet J Trop Med*, *3*(2), 2.

Baba, S. A., Malik, A. H., Wani, Z. A., Mohiuddin, T., Shah, Z., Abbas, N., & Ashraf, N. (2015). Phytochemical analysis and antioxidant activity of different tissue types of *Crocus sativus* and oxidative stress alleviating potential of saffron extract in plants, bacteria, and yeast. *South African Journal of Botany*, *99*, 80–87. doi:10.1016/j.sajb.2015.03.194

Babu, A., Pon, V., & Liu, D. (2008). Green tea catechins and cardiovascular health: An update. *Current Medicinal Chemistry*, *15*(18), 1840–1850. doi:10.2174/092986708785132979 PMID:18691042

Babu, N., Akash, Singh, A., & Navneet. (2018). Therapeutics potential and pharmacological properties of *Leucas indica*: A review. *The Pharma Innovation*, *7*(7), 564–568.

Babu, N., Pathak, V. M., & Singh, A. & Navneet. (2019). *Sonchus asper* leaves aqueous extract mediated synthesis of Titanium dioxide nanoparticles. *The Pharma Innovation*, *8*(4), 817–822.

Babu, N., Singh, A., Singh, R., & Navneet. (2017). A review on therapeutic potential and phytochemistry of *Tephrosia purpurea. Bulletin of Pure & Applied Sciences-Botany*, *36*(2), 91–104. doi:10.5958/2320-3196.2017.00013.1

Babycha, L., Devi, L. T., Singh, O. J., & Valte, V. (2013). The anticonvulsant effect of *Eupatorium birmanicum* DC leave extract alone and in combination with lamotrigine against MES seizure in albino mice. *Journal of Evolution of Medical and Dental Sciences*, *2*(38), 7250–7255. doi:10.14260/jemds/1288

Babycha, L., & Valte, V. (2018). Anticonvulsant activity of aqueous extract of *Eupatorium birmanicum* DC. Leaves on seizure induced by PTZ in albino mice, alone and in combination with ethosuximide. *International Journal of Pharmaceutical Sciences and Research*, *9*(5), 2048–2052.

Badar, V. A., Thawani, V. R., Wakode, P. T., Shrivastava, M. P., Gharpure, K. J., Hingorani, L. L., & Khiyani, R. M. (2005). Efficacy of *Tinospora cordifolia* in allergic rhinitis. *Journal of Ethnopharmacology*, *96*(3), 445–449. doi:10.1016/j.jep.2004.09.034 PMID:15619563

Bafna, P. A., & Balaraman, R. (2005). Anti-ulcer and antioxidant activity of pepticare, a herbomineral formulation. *Phytomedicine*, *12*(4), 264–270. doi:10.1016/j.phymed.2003.12.009 PMID:15898703

Bagatell, C. J., & Bremner, W. J. (1996). Androgens in men-uses and abuses. *The New England Journal of Medicine*, *334*(11), 707–715. doi:10.1056/NEJM199603143341107 PMID:8594431

Baird, J. K. (2009). Resistance to therapies for infection by *Plasmodium vivax. Clinical Microbiology Reviews*, *22*(3), 508–534. doi:10.1128/CMR.00008-09 PMID:19597012

Baird, R. D., Tan, D. S. P., & Kaye, S. B. (2010). Weekly paclitaxel in the treatment of recurrent ovarian cancer. *Clinical Oncology*, *7*(10), 575–582. PMID:20683437

Baker, C., Pradhan, A., Pakstis, L., Pochan, D. J., & Ismat, S. S. (2005). Synthesis and antibacterial properties of silver nanoparticles. *Journal of Nanoscience and Nanotechnology*, *5*(2), 244–249. doi:10.1166/jnn.2005.034 PMID:15853142

Balasundram, N., Sundram, K., & Samman, S. (2006). Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food Chemistry*, *99*(1), 191–203. doi:10.1016/j.foodchem.2005.07.042

Balzarini, J., Schols, D., Neyts, J., van Damme, E., Peumans, W., & de Clercq, E. (1991). α-(1–3)- and α-(1–6)-D-mannose-specific plant lectins are markedly inhibitory to human immunodeficiency virus and cytomegalovirus infections *in vitro. Antimicrobial Agents and Chemotherapy*, *35*(3), 410–416. doi:10.1128/AAC.35.3.410 PMID:1645507

Bamdad, F., Kadivar, M., & Keramat, J. (2006). Evaluation of phenolic content and antioxidant activity of Iranian caraway in comparison with clove and BHT using model systems and vegetable oil. *International Journal of Food Science & Technology*, *41*(s1), 20–27. doi:10.1111/j.1365-2621.2006.01238.x

Banerjee, P. S., Sharma, M., & Nema, R. K. (2009). Preparation, evaluation and hair growth stimulating activity of herbal hair oil. *Journal of Chemical and Pharmaceutical Research*, *1*, 261–267.

Banno, N., Akihisa, T., Yasukawa, K., Tokuda, H., Tabata, K., Nakamura, Y., & Suzuki, T. (2006). Anti-inflammatory activities of the triterpene acids from the resin of *Boswellia carteri. Journal of Ethnopharmacology*, *107*(2), 249–253. doi:10.1016/j.jep.2006.03.006 PMID:16621377

Bano, A., Ahmad, M., Hadda, T., Saboor, A., Sultana, S., Zafar, M., ... Ashraf, M. (2014). Quantitative ethnomedicinal study of plants used in the skardu valley at high altitude of Karakoram-Himalayan range, *Pakistan. Journal of Ethnobiology and Ethnomedicine*, *10*(1), 43. doi:10.1186/1746-4269-10-43 PMID:24885937

Bantle, J. P., Wylie-Rosett, J., Albright, A. L., Apovian, C. M., Clark, N. G., Franz, M. J., & Wheeler, M. L. (2008). Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care, 31*, S61-S78.

Bao, W., Li, K., Rong, S., Yao, P., Hao, L., Ying, C., ... Liu, L. (2010). Curcumin alleviates ethanol-induced hepatocytes oxidative damage involving heme oxygenase-1 induction. *Journal of Ethnopharmacology*, *128*(2), 549–553. doi:10.1016/j.jep.2010.01.029 PMID:20080166

Baquar, S. R. (1989). *Medicinal and Poisonous Plants of Pakistan*. Karachi, Pakistan: Printas.

Barrar, F. S. K. (2003). *Text book of pharmacology*. New Delhi: S. Chand.

Barry, H. (1999). Food-derived antioxidants. Evaluating their importance in food and in vivo. *Food Science and Agricultural Chemistry*, *1*(2), 67–109.

Bartneck, M., Keul, H. A., Singh, S., Czaja, K., Bornemann, J., Bockstaller, M., ... Groll, J. (2010). Rapid uptake of gold nanorods by primary human blood phagocytes and immunomodulatory effects of surface chemistry. *ACS Nano*, *4*(6), 3073–3086. doi:10.1021/nn100262h PMID:20507158

Barua, C. C., Talukdar, A., Begum, S. A., Pathak, D. C., Sarma, D. K., Borah, R. S., & Gupta, A. (2012). In vivo wound-healing efficacy and antioxidant activity of *Achyranthes aspera* in experimental burns. *Pharmaceutical Biology*, *50*(7), 892–899. doi:10.3109/13880209.2011.642885 PMID:22480137

Barua, C. C., Talukdar, A., Begum, S. A., Sarma, D. K., Pathak, D. C., Barua, A. G., & Bora, R. S. (2009). Wound healing activity of methanolic extract of leaves of *Alternanthera brasiliana* Kuntz using in vivo and in vitro model. *Indian Journal of Experimental Biology*, *47*, 1001–1005. PMID:20329705

Battu, G. R., Mamidipalli, S. N., Parimi, R., Viriyala, R. K., Patchula, R. P., & Mood, L. R. (2007). Hypoglycemic and anti-hyperglycemic effect of alcoholic extract of *Benincasa hispida* in normal and in alloxan induced diabetic rats. *Pharmacognosy Magazine*, *3*(10), 101.

Baur, A., Reski, R., & Gorr, G. (2005). Enhanced recovery of a secreted recombinant human growth factor using stabilizing additives and by coexpression of human serum albumin in the moss *Physcomitrella patens. Plant Biotechnology Journal*, *3*(3), 331–340. doi:10.1111/j.1467-7652.2005.00127.x PMID:17129315

Beck, M. (2010). Emerging drugs for lysosomal storage diseases. *Expert Opinion on Emerging Drugs*, *15*(3), 495–507. doi:10.1517/14728214.2010.498580 PMID:20557271

Beltran, J. C. M., & Stange, C. (2016). Apocarotenoids: A new carotenoid-derived pathway. *Sub-Cellular Biochemistry*, *79*, 239–272. doi:10.1007/978-3-319-39126-7_9 PMID:27485225

Benishin, C. G. (1992). Actions of ginsenoside Rb1 on choline uptake in central cholinergic nerve endings. *Neurochemistry International*, *21*(1), 1–5. doi:10.1016/0197-0186(92)90061-U PMID:1338897

Benzie, I. F. F. (2003). Evolution of dietary antioxidants. *Comparative Biochemistry and Physiology. Part A, Molecular & Integrative Physiology*, *136*(1), 113–126. doi:10.1016/S1095-6433(02)00368-9 PMID:14527634

Bernardini, S., Tiezzi, A., Laghezza Masci, V., & Ovidi, E. (2018). Natural products for human health: An historical overview of the drug discovery approaches. *Natural Product Research*, *32*(16), 1926–1950. doi:10.1080/14786419.2017.1356838 PMID:28748726

Bettaieb, I., Bourgou, S., Wannes, W. A., Hamrouni, I., Limam, F., & Marzouk, B. (2010). Essential oils, phenolics, and antioxidant activities of different parts of cumin (*Cuminum cyminum* L.). *Journal of Agricultural and Food Chemistry*, *58*(19), 10410–10418. doi:10.1021/jf102248j PMID:20809647

Bhalodia, Y. S., Patel, N. J., Patel, R. K., Vaghasiya, J. D., Jivani, N. P., & Sheth, N. R. (2009). *Benincasa cerifera* ameliorates renal ischemia/reperfusion injury in hyperlipidemic rat. *Pharmacognosy Research*, *1*(6), 406.

Bhatia, A. K., Kumar, A., Goel, A., Gupta, A., & Rahal, A. (2013). Antibacterial activity of hot aqueous extract of *Ocimum sanctum* leaves against common bacterial pathogens of animals. *Pharma Science Monitor*, *4*, 279–285.

Bhattacharya, S. K., & Muruganandam, A. V. (2003). Adaptogenic activity of *Withania somnifera:* An experimental study using a rat model of chronic stress. *Pharmacology, Biochemistry, and Behavior*, *75*(3), 547–555. doi:10.1016/S0091-3057(03)00110-2 PMID:12895672

Bhatt, I. D., Rawat, S., & Rawal, R. S. (2013). Antioxidants in medicinal plants. In *Biotechnology for Medicinal Plants* (pp. 295–326). Berlin: Springer Berlin Heidelberg. doi:10.1007/978-3-642-29974-2_13

Bhowmik, D., Chiranjib, Y. J., Tripathi, K. K., & Kumar, K. P. S. (2010). Herbal remedies of *Azadirachta indica* and its medicinal application. *Journal of Chemical and Pharmaceutical Research*, *2*(1), 62–72.

Bhowmik, D., Kumar, K. P. S., Srivastava, S., Paswan, S., Sankar, A., & Dutta, D. (2012). Traditional indian herbs punarnava and its medicinal importance. *Journal of Pharmacognosy and Phytochemistry*, *1*, 52–57.

Bilbis, L. S., Shehu, R. A., & Abubakar, M. G. (2002). Hypoglycemic and hypolipidemic effects of aqueous extract of *Arachis hypogaea* in normal and alloxan-induced diabetic rats. *Phytomedicine*, *9*(6), 553–555. doi:10.1078/09447110260573191 PMID:12403165

Bindhu, M. R., & Umadevi, M. (2014). Silver and gold nanoparticles for sensor and antibacterial applications. *Spectrochimica Acta. Part A: Molecular and Biomolecular Spectroscopy*, *128*, 37–45. doi:10.1016/j.saa.2014.02.119 PMID:24657466

Birari, R., Javia, V., & Bhutani, K. K. (2010). Antiobesity and lipid lowering effects of *Murraya koenigii* (L.) Spreng leaves extracts and mahanimbine on high fat diet induced obese rats. *Fitoterapia*, *81*(8), 1129–1133. doi:10.1016/j.fitote.2010.07.013 PMID:20655993

Birkner, K. M. (2006). Boswellia, the pain herb. *Pain and Stress Publications*, *1*(1), 60–61.

Birks, J., & Evans, J. G. (2009). *Ginkgo biloba* for cognitive impairment and dementia. *Cochrane Database of Systematic Reviews*, 1. doi:10.1002/14651858.CD003120.pub3 PMID:19160216

Birla, H., Keswani, C., Rai, S. N., Singh, S. S., Zahra, W., Dilnashin, H., ... Singh, S. P. (2019). Neuroprotective effects of *Withania somnifera* in BPA induced-cognitive dysfunction and oxidative stress in mice. *Behavioral and Brain Functions*, *15*(1), 9. doi:10.118612993-019-0160-4 PMID:31064381

Biswal, P. R., Sardar, K. K., Parija, S. C., Mishra, P. R., & Misra, S. N. (1997). Wound healing effect of *Eupatorium odoratum* Linn. and Himax in rabbits. *Indian Journal of Indigenous Medicines*, *19*(1), 71–74.

Bley, K. B., Boorman, G., Mohammad, B., McKenzie, D., & Babbar, S. A. (2012). Comprehensive review of the carcinogenic and anti-carcinogenic potential of *Capsaicin. Toxicologic Pathology*, *40*(6), 847–873. doi:10.1177/0192623312444471 PMID:22563012

Blumenthal, M., Goldberg, A., & Brinckmann, J. (2000). *Herbal Medicine. Expanded Commission E monographs*. Integrative Medicine Communications.

Boakye, M. K., Pietersen, D. W., Kotzé, A., Dalton, D. L., & Jansen, R. (2015). Knowledge and uses of African pangolins as a source of traditional medicine in Ghana. *PLoS One*, *10*(1), e0117199. doi:10.1371/journal.pone.0117199 PMID:25602281

Boehme, J. (1982). *Signature of all things*. Cambridge: James Clarke & Co.

Bores, G. M., Huger, F. P., Petko, W., Mutlib, A. E., Camacho, F., Rush, D. K., & Davis, L. (1996). Pharmacological evaluation of novel Alzheimer's disease therapeutics: Acetylcholinesterase inhibitors related to galanthamine. *The Journal of Pharmacology and Experimental Therapeutics*, *277*(2), 728–738. PMID:8627552

Borra, S. K., Lagisetty, R. K., & Mallela, G. R. (2011). Anti-ulcer effect of *Aloe vera* in non-steroidal anti-inflammatory drug induced peptic ulcers in rats. *African Journal of Pharmacy and Pharmacology*, *5*(16), 1867–1871.

Borrelli, F., Capasso, F., Capasso, R., Ascione, V., Aviello, G., Longo, R., & Izzo, A. A. (2006). Effect of *Boswellia serrata* on intestinal motility in rodents: Inhibition of diarrhea without constipation. *British Journal of Pharmacology*, *148*(4), 553–560. doi:10.1038j.bjp.0706740 PMID:16633355

Botanical Survey of India/Flora of India. (n.d.). efloraindia.nic.in

Bourne, C. R. (2014). Utility of the biosynthetic folate pathway for targets in antimicrobial discovery. *Antibiotics (Basel, Switzerland)*, *3*(1), 1–28. doi:10.3390/antibiotics3010001 PMID:27025730

Bozokalfa, K. M., Eşiyok, D., & Yağmur, B. (2011). Use of multivariate analysis in mineral accumulation of rocket (*Eruca sativa*) accessions. *Genetika*, *3*(3), 437–448. doi:10.2298/GENSR1103437B

Bradley, D. T., Zipfel, P. F., & Hughes, A. E. (2011). Complement in age-related macular degeneration: A focus on function. *Eye (London, England)*, *25*(6), 683–693. doi:10.1038/eye.2011.37 PMID:21394116

Bradwejn, J., Zhou, Y., Koszycki, D., & Shlik, J. (2000). A double-blind, placebo-controlled study on the effects of Gotu Kola (*Centella asiatica*) on acoustic startle response in healthy subjects. *Journal of Clinical Psychopharmacology*, *20*(6), 680–684. doi:10.1097/00004714-200012000-00015 PMID:11106141

Breusegem, F. V., & Dat, J. F. (2006). Reactive oxygen species in plant cell death. *Plant Physiology*, *141*(2), 384–390. doi:10.1104/pp.106.078295 PMID:16760492

Brewer, M. S. (2011). Natural Antioxidants: Sources, Compounds, Mechanisms of Action, and Potential Applications. *Comprehensive Reviews in Food Science and Food Safety*, *10*(4), 221–247. doi:10.1111/j.1541-4337.2011.00156.x

Brito, F. A., Lima, L. A., Ramos, M. F., Nakamura, M. J., Cavalher-Machado, S. C., Siani, A. C., ... Sampaio, A. L. (2007). Pharmacological study of anti-allergic activity of *Syzygium cumini* (L.) Skeels. *Brazilian Journal of Medical and Biological Research*, *40*(1), 105–115. doi:10.1590/S0100-879X2007000100014 PMID:17225003

Brooks, R. R., Chambers, M. F., Nicks, L. J., & Robinson, B. H. (1998). Phytomining. *Trends in Plant Science*, *3*(9), 359–362. doi:10.1016/S1360-1385(98)01283-7

Bruce-Chwatt, L. J., Black, R. H., Canfield, C. J., Clyde, D. F., Peters, W., Wernsdorfer, W. H., & World Health Organization. (1986). *Chemotherapy of malaria*. WHO.

Burgess, E. J., Larsen, L., & Perry, N. B. (2000). A Cytotoxic sesquiterpene caffeate from the Liverwort Bazzania n ovae-zelandiae. *Journal of Natural Products*, *63*(4), 537–539. doi:10.1021/np990492x PMID:10785435

Burgos-Morón, E., Calderón-Montaño, J. M., Salvador, J., Robles, A., & López-Lázaro, M. (2010). The dark side of curcumin. *International Journal of Cancer*, *126*(7), 1771–1775. PMID:19830693

Burygin, G. L., Khlebtsov, B. N., Shantrokha, A. N., Dykman, L. A., Bogatyrev, V. A., & Khlebtsov, N. G. (2009). On the enhanced antibacterial activity of antibiotics mixed with gold nanoparticles. *Nanoscale Research Letters*, *4*(8), 794–801. doi:10.100711671-009-9316-8 PMID:20596384

Butler, M. (2005). Animal cell cultures: Recent achievements and perspectives in the production of biopharmaceuticals. *Applied Microbiology and Biotechnology*, *68*(3), 283–291. doi:10.100700253-005-1980-8 PMID:15834715

Cai, Y. Z., Sun, M., Xing, J., Luo, Q., & Corke, H. (2006). Structure-radical scavenging activity relationships of phenolic compounds from traditional Chinese medicinal plants. *Life Sciences*, *78*(25), 2872–2888. doi:10.1016/j.lfs.2005.11.004 PMID:16325868

Cai, Y., Luo, Q., Sun, M., & Corke, H. (2004). Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. *Life Sciences*, *74*(17), 2157–2184. doi:10.1016/j.lfs.2003.09.047 PMID:14969719

Cameron, E., & Pauling, L. (1976). Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proceedings of the National Academy of Sciences of the United States of America*, *73*(10), 3685–3689. doi:10.1073/pnas.73.10.3685 PMID:1068480

Cao, H., Polansky, M. M., & Anderson, R. A. (2007). Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. *Archives of Biochemistry and Biophysics*, *459*(2), 214–222. doi:10.1016/j.abb.2006.12.034 PMID:17316549

Carraz, M., Jossang, A., Franetich, J. F., Siau, A., Ciceron, L., Hannoun, L., & Mazier, D. (2006). A plant-derived morphinan as a novel lead compound active against malaria liver stages. *PLoS Medicine*, *3*(12), 2392–2402. doi:10.1371/journal.pmed.0030513 PMID:17194195

Carville, K. (2008). Principles of best practice: Wound infection in clinical practice. An international consensus. World Union of Wound Healing Societies, 1-12.

Cassileth, B. (2010). Turmeric (*Curcuma longa, Curcuma domestica*). *Oncology*, *24*(6). PMID:20568597

Castellanos, G. J. R., Prieto, J. M., & Heinrich, M. (2009). Red Lapacho (*Tabebuia impetiginosa*)-a global ethnopharmacological commodity? *Journal of Ethnopharmacology*, *121*(1), 1–13. doi:10.1016/j.jep.2008.10.004 PMID:18992801

Castillo, A. L., Ramos, J. D., De Francia, J. L., Quilala, P. F., & Dujunco, M. U. (2014). Immunomodu latory effects of *Tinospora cordifolia* lotion on interleukin-1, interleukin-6 and interleukin-8 levels in scabies-infected paediatric patients: A single blind, randomized trial. *International Journal of Pharmaceutical Sciences and Drug Research*, *6*(3), 204–210.

Chai, J. (2011). *Peptic Ulcer Disease*. Rijeka, Croatia: Academic Press. doi:10.5772/749

Chakravarthi, K. K., & Avadhani, R. (2013). Beneficial effect of aqueous root extract of *Glycyrrhiza glabra* on learning and memory using different behavioral models: An experimental study. *Journal of Natural Science, Biology, and Medicine*, *4*(2), 420–425. doi:10.4103/0976-9668.117025 PMID:24082744

Chandra, S., Chandra, D., Barh, A., Pankaj, Pandey, R. K., & Sharma, I. P. (2017). Bryophytes: Hoard of remedies, an ethno-medicinal review. *Journal of Traditional and Complementary Medicine*, *7*(1), 94–98. doi:10.1016/j.jtcme.2016.01.007 PMID:28053893

Chand, S., & Dave, R. (2009). *In vitro* models for antioxidant activity evaluation and some medicinal plants possessing antioxidant properties: An overview. *African Journal of Microbiological Research*, *3*, 981–996.

Chang, Y. S., & Lin, I. H. (2003). Compendium of medicinal plants used by the indigenous people of Taiwan. Department of Health, Executive Yuan, Taipei, Taiwan.

Chattopadhyay, R. R. (1993). Hypoglycemic effect of *Ocimum sanctum* leaf extract in normal and streptozotocin diabetic rats. *Indian Journal of Experimental Biology*, *31*(11), 891–893. PMID:8112763

Chattopadhyay, R. R., Bhattacharyya, S. K., Medda, C., Chanda, S., Datta, S., & Pal, N. K. (2007). Antibacterial activity of black myrobalan (Fruit of *Terminalia chebula* Retz.) against uropathogen *Escherichia coli. Phcog. Rev*, *3*(11), 212–215.

Chaturvedi, A., Kumar, M. M., Bhawani, G., Chaturvedi, H., Kumar, M., & Goel, R. K. (2007). Effect of ethanolic extract of *Eugenia jambolana* seeds on gastric ulceration and secretion in rats. *Indian Journal of Physiology and Pharmacology*, *51*(2), 131–141. PMID:18175656

Chaudhuri, A. K., Pal, S., Gomes, A., & Bhattacharya, S. (1990). Anti-inflammatory and related actions of *Syzygium cuminii* seed extract. *Phytotherapy Research*, *4*(1), 5–10. doi:10.1002/ptr.2650040103

Chauhan, S. (2013). An overview on blood purifier. *International Research Journal of Pharmacy*, *4*(9), 8–10. doi:10.7897/2230-8407.04903

Chen, C., Xiao, W., Huang, L., Yu, G., Ni, J., Yang, L., ... Hu, G. (2017). Shikonin induces apoptosis and necroptosis in pancreatic cancer via regulating the expression of RIP1/RIP3 and synergizes the activity of gemcitabine. *American Journal of Translational Research*, *9*(12), 5507–5517. PMID:29312502

Cheng, A., Sun, L., Wu, X., & Lou, H. (2001). The inhibitory effect of a monocyclic bisbibenzylricardin D on the biofilms of *Candida albicans. Biological & Pharmaceutical Bulletin*, *32*(8), 1417–1421. doi:10.1248/bpb.32.1417 PMID:19652383

Chen, J. H., & Ho, C. T. (1997). Antioxidant Activities of Caffeic Acid and Its Related Hydroxycinnamic Acid Compounds. *Journal of Agricultural and Food Chemistry*, *45*(7), 2374–2378. doi:10.1021/jf970055t

Chen, J. J., Tsai, Y. C., Hwang, T. L., & Wang, T. C. (2011). Thymol, benzofuranoid, and phenylpropanoid derivatives: Anti-inflammatory constituents from *Eupatorium cannabinum. Journal of Natural Products*, *74*(5), 1021–1027. doi:10.1021/np100923z PMID:21391659

Chen, L. C., Lee, T. H., Sung, P. J., Shu, C. W., Lim, Y. P., Cheng, M. J., ... Chen, J. J. (2014). New thymol derivatives and cytotoxic constituents from the root of *Eupatorium cannabinum*s sp. *asiaticum. Chemistry & Biodiversity*, *11*(9), 1374–1380. doi:10.1002/cbdv.201300392 PMID:25238078

Chen, W. W., Zhang, X. I. A., & Huang, W. J. (2016). Role of neuroinflammation in neurodegenerative diseases. *Molecular Medicine Reports*, *13*(4), 3391–3396. doi:10.3892/mmr.2016.4948 PMID:26935478

Chen, X., & Pan, W. (2014). The treatment strategies for neurodegenerative diseases by integrative medicine. *Integrative Medicine International*, *1*(4), 223–225. doi:10.1159/000381546

Chen, Y., Chen, Z. Y., Chen, L., Zhang, J. Y., Fu, L. Y., Tao, L., ... Shen, X. C. (2019). Shikonin inhibits triple-negative breast cancer-cell metastasis by reversing the epithelial-to-mesenchymal transition via glycogen synthase kinase 3β-regulated suppression of β-catenin signalling. *Biochemical Pharmacology*, *166*, 33–45. doi:10.1016/j.bcp.2019.05.001 PMID:31071331

Cheypratub, P., Leeanansaksiri, W., & Eumkeb, G. (2018). The synergy and mode of action of *Cyperus rotundus* L. extract plus ampicillin against ampicillin-resistant *Staphylococcus aureus. Evidence-Based Complementary and Alternative Medicine*, *2018*, 1–11. doi:10.1155/2018/3438453 PMID:29849704

Chianese, G., Yerbanga, S. R., Lucantoni, L., Habluetzel, A., Basilico, N., Taramelli, D., ... Taglialatela-Scafati, O. (2010). Antiplasmodial triterpenoids from the fruits of neem, *Azadirachta indica. Journal of Natural Products*, *73*(8), 1448–1452. doi:10.1021/np100325q PMID:20669933

Chiu, N. Y., & Chang, K. H. (2001). The illustrated medicinal plants of Taiwan. SMC Publishing Inc.

Chizick, S., & Delorscio, R. (1999). *Natural preparation for treatment of male pattern hair loss*. Google Patents.

Choi, B.-M., Kim, H.-J., Oh, G.-S., Pae, H.-O., Oh, H., Jeong, S., & Chung, H.-T. (2002). 1, 2, 3, 4, 6-Penta-O-galloyl-beta-D-glucose protects rat neuronal cells (Neuro 2A) from hydrogen peroxide-mediated cell death via the induction of heme oxygenase-1. *Neuroscience Letters*, *328*(2), 185–189. doi:10.1016/S0304-3940(02)00513-X PMID:12133584

Choi, J., Lee, K. T., Ka, H., Jung, W. T., Jung, H. J., & Park, H. J. (2001). Constituents of the essential oil of the *Cinnamomum cassia* stem bark and the biological properties. *Archives of Pharmacal Research*, *24*(5), 418–423. doi:10.1007/BF02975187 PMID:11693543

Chopda, M. Z., & Mahajan, R. T. (2009). Wound healing plants of Jalgaon district of Maharashtra state, India. *Ethnobotanical Leaflets*, *13*, 1–32.

Chopra, A. (2000). Ayurvedic Medicine and Arthritis. *Rheumatic Disease Clinics*, *26*(1), 133–144. doi:10.1016/S0889-857X(05)70127-7 PMID:10680201

Chopra, R. N., Chopra, I. C., & Varma, B. S. (1969). *Glossary of Indian Medicinal Plants/ Supplement*. Council of Scientific & Industrial Research.

Chou, C.-H., Gong, C.-L., Chao, C.-C., Lin, C.-H., Kwan, C.-Y., Hsieh, C.-L., & Leung, Y.-M. (2009). Rhynchophylline from *Uncaria rhynchophylla* functionally turns delayed rectifiers into A-Type K+ channels. *Journal of Natural Products*, *72*(5), 830–834. doi:10.1021/np800729q PMID:19331340

Chowdhary, N., Kaur, M., Singh, A., & Kumar, B. (2014). Wound healing activity of aqueous extracts of *Ficus religiosa* and *Ficus benghalensis* leaves in rats. *Indian Journal of Research in Pharmacy and Biotechnology*, *2*(2), 1071–1081.

Chow, J. M., Huang, G. C., Shen, S. C., Wu, C. Y., Lin, C. W., & Chen, Y. C. (2008). Differential apoptotic effect of wogonin and nor-wogonin via stimulation of ROS production in human leukemia cells. *Journal of Cellular Biochemistry*, *103*(5), 1394–1404. doi:10.1002/jcb.21528 PMID:17955493

Chrubasik, J. E., Roufogalis, B. D., Wagner, H., & Chrubasik, S. (2007). A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: Urticae radix. *Phytomedicine*, *14*(7-8), 568–579. doi:10.1016/j.phymed.2007.03.014 PMID:17509841

Chuang, C. Y., Hsu, C., Chao, C. Y., Wein, Y. S., Kuo, Y. H., & Huang, C. J. (2006). Fractionation and identification of 9c, 11t, 13t-conjugated linolenic acid as an activator of PPARα in bitter gourd (*Momordica charantia* L.). *Journal of Biomedical Science*, *13*(6), 763–772. doi:10.100711373-006-9109-3 PMID:16955349

Chulet, R., & Pradhan, P. (2009). A review on rasayana. *Pharmacognosy Reviews*, *3*(6), 229.

Chung, I.-W., Moore, N. A., Oh, W.-K., O'Neill, M. F., Ahn, J.-S., Park, J.-B., ... Kim, Y. S. (2002). Behavioural pharmacology of polygalasaponins indicates potential antipsychotic efficacy. *Pharmacology, Biochemistry, and Behavior*, *71*(1-2), 191–195. doi:10.1016/S0091-3057(01)00648-7 PMID:11812522

Clark, R., & Lee, S. (2016). Anticancer properties of *Capsaicin* against human cancer. *Anticancer Research*, *36*, 837–844. PMID:26976969

Clavin, M., Gorzalczany, S., Macho, A., Munoz, E., Ferraro, G., Acevedo, C., & Martino, V. (2007). Anti-inflammatory activity of flavonoids from *Eupatorium arnottianum. Journal of Ethnopharmacology*, *112*(3), 585–589. doi:10.1016/j.jep.2007.04.007 PMID:17570627

Cordell, G. A. (2000). Biodiversity and drug discovery -a symbiotic relationship. *Phytochemistry*, *55*(6), 463–480. doi:10.1016/S0031-9422(00)00230-2 PMID:11130658

Costescu, C. I., Hădărugă, N. G., Rivis, A., Hădărugă, D. I., Lupea, A. X., & Pârvu, D. (2008). Antioxidant activity evaluation of some *Matricaria chamomilla* L. extracts. *Journal of Agroalimentary Processes and Technologies*, *14*, 417–432.

Cox, R. F., & Morgan, M. P. (2013). Microcalcifications in breast cancer: Lessons from physiological mineralization. *Bone*, *53*(2), 437–450. doi:10.1016/j.bone.2013.01.013 PMID:23334083

Crane, P. K., & Doody, R. S. (2009). Donepezil treatment of patients with MCI: A 48-week randomized, placebo-controlled trial. *Neurology*, *73*(18), 1514–1516. doi:10.1212/WNL.0b013e3181bd6c25 PMID:19884584

Creagan, E. T., Moertel, C. G., O'Fallon, J. R., Schutt, A. J., O'Connell, M. J., Rubin, J., & Frytak, S. (1979). Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer: A controlled trial. *The New England Journal of Medicine*, *301*(13), 687–690. doi:10.1056/NEJM197909273011303 PMID:384241

Crowther, C. A., Hiller, J. E., Moss, J. R., McPhee, A. J., Jeffries, W. S., & Robinson, J. S. (2005). Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *The New England Journal of Medicine*, *352*(24), 2477–2486. doi:10.1056/NEJMoa042973 PMID:15951574

Crulckshanks, K. J., Orchard, T. J., & Becker, D. J. (1985). The cardiovascular risk profile of adolescents with insulin-dependent diabetes mellitus. *Diabetes Care*, *8*(2), 118–124. doi:10.2337/diacare.8.2.118 PMID:3996168

Cui, L., Wang, Z., Miao, J., Miao, M., Chandra, R., Jiang, H., & Cui, L. (2012). Mechanisms of in vitro resistance to dihydroartemisinin in *Plasmodium falciparum. Molecular Microbiology*, *86*(1), 111–128. doi:10.1111/j.1365-2958.2012.08180.x PMID:22812578

Da Silva, A. F., & Benchimol, J. L. (2014). Malaria and quinine resistance: A medical and scientific issue between Brazil and Germany (1907–19). *Medical History*, *58*(1), 1–26. doi:10.1017/mdh.2013.69 PMID:24331212

Daisy, P. (2007). *A process for preparation of a novel compound 5,6-dihydroxy- 3-[(4-hydroxy-6-(hydroxymethyl)-3,5-di[3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2h-2pyranyl} oxytrtahydro-2h-2pranyl)oxy]2methoxy10,13dimethylperhycyclopenta[aphenanthren-17-yl [phenyl]methyl acetate from Syzygium cumini (L.) skeels seeds with antibacterial and antidiabetic activity*. Patent Application No.810/CHE/2007.

Damle, M. (2014). *Glycyrrhiza glabra* (Liquorice) potent medicinal herb. *Indian Journal of Herbal Medicine*, *2*(2), 132–136.

Dar, A. I., Saxena, R. C., Matadeen, B., Barela, B., & Jadhaw, V. (2013). Toxicity of *Eupatorium cannabinum* L. against second and fourth instar larvae of *Culex quinquefasciatus* and *Aedes aegypti*. *International Journal of Research in Ayurveda and Pharmacy*, *4*(1), 63–66. doi:10.7897/2277-4343.04126

Dar, M. S., Joo, N., & Ganaie, S. A. (2018). Medicinal plants used by tribal and rural community of Sata Pokhran area of tehsil Pampore of district Pulwama, Jammu and Kashmir-India. *Journal of Phytopharmacology*, *7*(1), 66–71.

Dar, P. A., Mir, S. A., Bhat, J. A., Hamid, A., Singh, L. R., Malik, F., & Dar, T. A. (2019). An anti-cancerous protein fraction from *Withania somnifera* induces ROS-dependent mitochondria-mediated apoptosis in human MDA-MB-231 breast cancer cells. *International Journal of Biological Macromolecules*, *135*, 77–87. doi:10.1016/j.ijbiomac.2019.05.120 PMID:31121227

Dar, P. A., Singh, L. R., Kamal, M. A., & Dar, T. A. (2016). Unique Medicinal Properties of *Withania somnifera*: Phytochemical Constituents and Protein Component. *Current Pharmaceutical Design*, *22*(5), 535–540. doi:10.2174/1381612822666151125001751 PMID:26601969

Dash, B. (1991). *Materia Medica of Ayurveda* (Vol. B). New Delhi: Jain Publishers.

Dash, G. K., & Murthy, P. N. (2011). Studies on wound healing activity of *Heliotropium indicum* Linn. leaves on rats. *ISRN Pharmacology*, *2011*, 1–8. doi:10.5402/2011/847980 PMID:22084720

Das, S., & Sarme, G. (2009). Study of the hepatoprotective activity of the ethanolic extract of the pulp of *Eugenia jambolana* (Jamun) in albino rats. *Journal of Clinical and Diagnostic Research: JCDR*, *3*, 1466–1474.

Das, S., Vasudeva, N., & Sharma, S. (2016). *Cichorium intybus*: A concise report on its ethnomedicinal, botanical and phytopharmacological aspects. *Drug Design, Development and Therapy*, *7*(1), 1–12. doi:10.4103/2394-6555.180157

Dastmalchi, K. D., Dorman, H. J., Koşar, M., & Hiltunen, R. (2007). Chemical composition and i*n vitro* antioxidant evaluation of a water-soluble moldavian balm (*Dracocephalum moldavica* L.) extract. *Lebensmittel-Wissenschaft + Technologie*, *40*(2), 239–248. doi:10.1016/j.lwt.2005.09.019

Datir, S. B., Ganjare, A. B., Nirmal, S. A., Bhawar, S. B., Bharati, D. K., & Patil, M. J. (2009). Evaluation of antiallergic activity of the various extracts of the aerial part of *Achyranthes aspera* var. *Porphyristachya* (wall. Ex moq.) Hook. f. *Pharmacologyonline*, *3*, 921–925.

Datta, K., Singh, A. T., Mukherjee, A., Bhat, B., Ramesh, B., & Burman, A. C. (2009). *Eclipta alba* extract with potential for hair growth promoting activity. *Journal of Ethnopharmacology*, *124*(3), 450–456. doi:10.1016/j.jep.2009.05.023 PMID:19481595

David, B., Wolfender, J. L., & Dias, D. A. (2015). The pharmaceutical industry and natural products: Historical status and new trends. *Phytochemistry Reviews*, *14*(2), 299–315. doi:10.100711101-014-9367-z

David, E. S. (1964). Indigenous uses of turmeric (*Curcuma domestica*) in Asia and Oceania. *ANTHROPOS: International Review of Anthropology and Linguistics*, *59*, 93–127.

D'cunha. (2015). *Purify your blood naturally with these five Herbs*. Academic Press.

De Lima, T. C., Klüeger, P. A., Pereira, P. A., Macedo-Neto, W. P., Morato, G. S., & Farias, M. R. (1998). Behavioural effects of crude and semi-purified extracts of *Syzygium cuminii* Linn. Skeels. *Phytotherapy Research*, *12*(7), 488–493. doi:10.1002/(SICI)1099-1573(199811)12:7<488::AID-PTR344>3.0.CO;2-0

Deba, F., Xuan, T. D., Yasuda, M., & Tawata, S. (2013). Chemical composition and antioxidant, antibacterial and antifungal activities of the essential oils from *Bidens pilosa* Linn. var. Radiata. *Food Control*, *19*(4), 246–352.

Decker, E. L., & Reski, R. (2008). Current achievements in the production of complex biopharmaceuticals with moss bioreactors. *Bioprocess and Biosystems Engineering*, *31*(1), 3–9. doi:10.100700449-007-0151-y PMID:17701058

Deepak, A. S. A. (2008). *Indigenous Herbal Medicines: Tribal Formulations and Traditional Herbal Practices*. Jaipur, India: Aavishkar Publishers Distributor.

Demain, A. L. (2014). Importance of microbial natural products and the need to revitalize their discovery. *Journal of Industrial Microbiology & Biotechnology*, *41*(2), 185–201. doi:10.100710295-013-1325-z PMID:23990168

Demilew, W., Adinew, G. M., & Asrade, S. (2018). Evaluation of the wound healing activity of the crude extract of leaves of *Acanthus polystachyus* Delile (Acanthaceae). *Evidence-Based Complementary and Alternative Medicine*, *2018*, 1–9. doi:10.1155/2018/2047896 PMID:29991951

Deng, X., Chen, Q., Qiang, L., Chi, M., Xie, N., Wu, Y., ... Xie, Y. (2018). Development of a porcine full-thickness burn hypertrophic scar model and investigation of the effects of shikonin on hypertrophic scar remediation. *Frontiers in Pharmacology*, *9*, 590. doi:10.3389/fphar.2018.00590 PMID:29922164

Desai, A. K., & Grossberg, G. T. (2005). Diagnosis and treatment of Alzheimer's disease. *Neurology*, *64*(12suppl 3), 34–39. doi:10.1212/WNL.64.12_suppl_3.S34 PMID:15994222

Deshmukh, P. T., Fernandes, J., Atul, A., & Toppo, E. (2009). Wound healing activity of *Calotropis gigantea* root bark in rats. *Journal of Ethnopharmacology*, *125*(1), 178–181. doi:10.1016/j.jep.2009.06.007 PMID:19539020

Deshpande, P. K., Gothalwal, R., & Pathak, A. K. (2014). Phytochemical analysis and evaluation of antimalarial activity of *Azadirachta indica. The Pharma Innovation*, *3*(9, Part A), 12.

Deshpande, S. S., Shah, G. B., & Parmar, N. S. (2003). Antiulcer activity of *Tephrosia purpurea* in rats. Ind. *Journal of Pharmaceutics*, *35*, 168–172.

Dessy, V. J., & Sivakumar, S. R. (2019). Clonal propagation of *Curcuma aeruginosa Roxb*.: A versatile medicinal plant. *Medicinal Plants-International Journal of Phytomedicines and Related Industries*, *11*(1), 67–72. doi:10.5958/0975-6892.2019.00008.X

Devi, L. R., Singh, T. S., & Laitonjam, W. S. (2007). Antifungal and phytochemical studies of *Eupatorium birmanicum* DC. *Indian Journal of Chemistry*, *46B*, 1868–1872.

Devi, O. J., & Chhetry, G. K. N. (2013). Evaluation of antifungal properties of certain plants against *Drechslera oryzae* causing brown leaf spot of rice in Manipur valley. *International Journal of Scientific and Research Publications*, *3*(5), 1.

Devi, T. H. I., Devi, K. H. U., & Singh, E. J. (2015). Wild medicinal plants in the hill of Manipur, India: A traditional therapeutic potential. *International Journal of Scientific and Research Publications*, *5*(6), 1–9.

Devmurari, V. P. (2010). Phytochemical screening study and antibacterial evaluation of *Symplocos racemosa* Roxb. *Archives of Applied Science Research*, *2*(1), 354–359.

Dey, A. (2011). Phytochemistry and pharmacology: A concise review. *Journal of Applied Pharmaceutical Science*, *1*(6), 51–57.

Dey, A., & Mukherje, A. (2015). Therapeutic potential of bryophytes and derived compounds against cancer. *Journal of Acute Disease*, *4*(3), 236–248. doi:10.1016/j.joad.2015.04.011

Dhale, D. A., & Bhoi, S. (2013). Pharmacognostic Characterization and Phytochemical Screening of *Achyranthes aspera* Linn. *Current Agriculture Research Journal*, *1*(1), 51–57. doi:10.12944/CARJ.1.1.07

Dhanasekaran, M., Baskar, A. A., Ignacimuthu, S., Agastian, P., & Duraipandiyan, V. (2009). Chemopreventive potential of Epoxy clerodane diterpene from *Tinospora cordifolia* against diethyl nitrosamine-induced hepatocellular carcinoma. *Investigational New Drugs*, *27*(4), 347–355. doi:10.100710637-008-9181-9 PMID:18853103

Dhanasekaran, M., Holcomb, L. A., Hitt, A. R., Tharakan, B., Porter, J. W., Young, K. A., & Manyam, B. V. (2009). *Centella asiatica* extract selectively decreases amyloid β levels in hippocampus of Alzheimer's disease animal model. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *23*(1), 14–19. doi:10.1002/ptr.2405 PMID:19048607

Dhanotia, R., Chauhan, N. S., Saraf, D. K., & Dixit, V. K. (2011). Effect of *Citrullus colocynthis* Schrad fruits on testosterone-induced alopecia. *Natural Product Research*, *25*(15), 1432–1443. doi:10.1080/14786410802632820 PMID:19764005

Dhawan, B. N., Patnaik, G. K., Rastogi, R. P., Singh, K. K., & Tandon, J. S. (1977). Screening of Indian plants for biological activity: Part VI. *Indian Journal of Experimental Biology*, *15*(3), 208–219. PMID:914326

Dhayalan, M., Denison, M. I. J., Ayyar, M., Gandhi, N. N., Krishnan, K., & Baykal, A. (2018). Biogenic synthesis, characterization of gold and silver nanoparticles from Coleus forskohlii and their clinical importance. *Journal of Photochemistry & Photobiology*, *183*, 251–257. doi:10.1016/j.jphotobiol.2018.04.042 PMID:29734113

Dhingra, A. K., Chopra, B., & Mittal, S. K. (2013). *Martynia annua* L.: A review on its ethnobotany, phytochemical and pharmacological profile. *Journal of Pharmacognosy and Phytochemistry*, *1*, 135–140.

Di Carli, M. F., Janisse, J., Ager, J., & Grunberger, G. (2003). Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *Journal of the American College of Cardiology*, *41*(8), 1387–1393. doi:10.1016/S0735-1097(03)00166-9 PMID:12706936

Dias, D. A., Urban, S., & Roessner, U. (2012). A historical overview of natural products in drug discovery. *Metabolites*, *2*(2), 303–336. doi:10.3390/metabo2020303 PMID:24957513

Ding, H. Y., Chou, T. H., & Liang, C. H. (2010). Antioxidant and antimelanogenic properties of rosmarinic acid methyl ester from *Origanum vulgare. Food Chemistry*, *123*(2), 254–262. doi:10.1016/j.foodchem.2010.04.025

Divakar, M. C., Rao, S. B., Nair, G. R. N., & Hisham, A. (2001). The role of fatty acids on the ulcer healing property of the nimbidin fraction of the neem oil. *Journal of Medicinal and Aromatic Plants Science*, *23*(3), 404–408.

Djipa, C. D., Delmee, M., & Quetin-Leclercq, J. (2000). Antimicrobial activity of bark extracts of *Syzygium jambos* (L.) Alston (Myrtaceae). *Journal of Ethnopharmacology*, *71*(1-2), 307–313. doi:10.1016/S0378-8741(99)00186-5 PMID:10904178

Dobos, G. J., Tan, L., Cohen, M. H., McIntyre, M., Bauer, R., Li, X., & Bensoussan, A. (2005). Are national quality standards for traditional Chinese herbal medicine sufficient? Current governmental regulations for traditional Chinese herbal medicine in certain Western countries and China as the Eastern origin country. *Complementary Therapies in Medicine*, *13*(3), 183–190. doi:10.1016/j.ctim.2005.06.004 PMID:16150372

Dong, J. C. (2013). The Relationship between Traditional Chinese Medicine and Modern Medicine. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–10. doi:10.1155/2013/153148 PMID:23983772

Dorsey, G., Kamya, M. R., Singh, A., & Rosenthal, P. J. (2001). Polymorphisms in the *Plasmodium falciparum* pfcrt and pfmdr-1 genes and clinical response to chloroquine in Kampala, Uganda. *The Journal of Infectious Diseases*, *183*(9), 1417–1420. doi:10.1086/319865 PMID:11294677

Drenth, J., Jansonius, J. N., Koekoek, R., & Wolthers, B. G. (1971). The structure of papain. *Advances in Protein Chemistry*, *25*, 79–115. doi:10.1016/S0065-3233(08)60279-X PMID:4946704

Drever, B. D., Anderson, W. G. L., Riedel, G., Kim, D. H., Ryu, J. H., Choi, D.-Y., & Platt, B. (2008). The seed extract of *Cassia obtusifolia* offers neuroprotection to mouse hippocampal cultures. *Journal of Pharmacological Sciences*, *107*(4), 380–392. doi:10.1254/jphs.08034FP PMID:18719316

Duke, J. A., Bogenschutz-Godwin, M. J., Ducelliar, J., & Duke, P. A. K. (2002). *Handbook of Medicinal Herbs*. Boca Raton, FL: CRC Press. doi:10.1201/9781420040463

Dulal, M. S. R., Taher, M. A., & Hossain, M. A. (2019). Antioxidant phytochemicals and some research on plants-A review. *World Journal of Pharmaceutical and Medical Research*, *5*(3), 40–45.

Dutta, B., & Mahanta, B. (2016). Studies on secondary metabolites, total phenol and flavonoid contents of *Eupatorium cannabinum* L. in Assam, India. *Journal of Medicinal Plants Studies*, *4*(2), 130–133.

Dwajani, S., & Shanbhag, T. (2008). *Michelia champaca*: Wound healing activity in immunosuppressed rats. *The Internet Journal of Alternative Medicine*, *7*(2), 1–5.

Dwivedi, D., Dwivedi, M., Malviya, S., & Singh, V. (2017). Evaluation of wound healing, antimicrobial and antioxidant potential of *Pongamia pinnata* wistar rats. *J of Trad and Comp Med*, *7*(1), 79–85. PMID:28053891

Dzib-Guerra, W. D. C., Escalante-Erosa, F., Garcia-Sosa, K., Derbre, S., Blanchard, P., Richomme, P., & Pena-Rodriguez, L. M. (2016). Anti-advanced glycation end-product and free radical scavenging activity of plants from the yucatecan flora. *Pharmacognosy Research*, *8*(4), 276. doi:10.4103/0974-8490.188883 PMID:27695268

Ebling, F. J. (1987). The biology of hair. *Dermatologic Clinics*, *5*(3), 467–481. doi:10.1016/S0733-8635(18)30728-9 PMID:3301105

Edgar, J. A., Lin, H. J., Kumana, C. R., & Ng, M. M. (1992). Pyrrolizidine alkaloid composition of three Chinese medicinal herbs, *Eupatorium cannabinum, E. japonicum* and *Crotalaria assamica. The American Journal of Chinese Medicine*, *20*(3-4), 281–288. doi:10.1142/S0192415X92000291 PMID:1471612

Ehiowemwenguan, G., Emoghene, A. O., & Inetianbor, J. E. (2014). Antibacterial and phytochemical analysis of banana fruit peel. *IOSR Journal of Pharmacy*, *4*(8), 18–25. doi:10.9790/3013-0408018025

Elavathagan, T., & Arunachalam, K. D. (2011). Memecylon edule leaf extract mediated green synthesis of silver and gold nanoparticles. *International Journal of Nanomedicine*, *6*, 1265–1278. doi:10.2147/IJN.S18347 PMID:21753878

Eldeen, I. M. S., Van Heerden, F. R., & Van Staden, J. (2010). *In vitro* biological activities of niloticane, a new bioactive cassane diterpene from the bark of *Acacia nilotica* subsp. kraussiana. *Journal of Ethnopharmacology*, *128*(3), 555–560. doi:10.1016/j.jep.2010.01.057 PMID:20138134

Elekofehinti, O. O., Adanlawo, I. G., Salin, J. A., & Sodehinde, S. A. (2012). Saponins from *Solanum anguivi* fruits extracts hypolipidemic potential in Rattusnovergicus. *Der Pharmacia Lettre.*, *4*(3), 811–814.

Elema, E. T., Schripsema, J., & Malingrd, T. M. (1989). Flavones and flavonol glycosides from *Eupatorium cannabinum* L. *Pharmaceutisch Weekblad Sci*, *11*(5), 161–164. doi:10.1007/BF01959464 PMID:2594467

Elias, M. E. A., Schroth, G., Macêdo, J. L. V., Mota, M. S. S., & Angelo, S. A. (2002). Mineral nutrition, growth and yields of annatto trees (*Bixa orellana*) in agroforestry on an Amazonian Ferralsol. *Experimental Agriculture*, *38*(3), 277–289. doi:10.1017/S0014479702003034

Elmore, S. (2007). Apoptosis: A review of programmed cell death. *Toxicologic Pathology*, *35*(4), 495–516. doi:10.1080/01926230701320337 PMID:17562483

Elnagar, A. Y., Sylvester, P. W., & El Sayed, K. A. (2011). (−)-Oleocanthal as a c-Met inhibitor for the control of metastatic breast and prostate cancers. *Planta Medica*, *77*(10), 1013–1019. doi:10.1055-0030-1270724 PMID:21328179

Ernst, E. (2008). Frankincense: Systematic review. *BMJ (Clinical Research Ed.)*, *337*(dec17 2), 2813. doi:10.1136/bmj.a2813 PMID:19091760

Escalona-Arranz, J. C., Peres-Roses, R., Urdaneta-Laffita, I., Camacho-Pozo, M. I., Rodriguez-Amado, J., & Licea-Jimenez, I. (2010). Antimicrobial activity of extracts from *Tamarindus indica* L. leaves. *Pharm. Mag*, *6*(23), 242–247. doi:10.4103/0973-1296.66944 PMID:20931087

Esmaeelpanah, E., Razavi, B. M., Vahdati Hasani, F., & Hosseinzadeh, H. (2018). Evaluation of epigallocatechin gallate and epicatechin gallate effects on acrylamide-induced neurotoxicity in rats and cytotoxicity in PC 12 cells. *Drug and Chemical Toxicology*, *41*(4), 441–448. doi:10.1080/01480545.2017.1381108 PMID:29072525

Fabricant, D. S., & Farnsworth, N. R. (2001). The value of plants used in traditional medicine for drug Discovery. *Environmental Health Perspectives*, *109*, 69–75. PMID:11250806

Fang, F., Kennedy, J., Carder, D. A., Futter, J., Murmu, P., & Markwitz, A. (2010). Modulation of field emission properties of ZnO nanorods during arc discharge. *Journal of Nanoscience and Nanotechnology*, *10*(12), 8239–8243. doi:10.1166/jnn.2010.3009 PMID:21121322

Fatima, F., Bajpai, P., Pathak, N., Singh, S., Priya, S., & Verma, S. R. (2015). Antimicrobial and immunomodulatory efficacy of extracellularly synthesized silver and gold nanoparticles by a novel phosphate solubilizing fungus *Bipolaris tetramera. BMC Microbiology*, *15*(1), 52–61. doi:10.118612866-015-0391-y PMID:25881309

Favela-Hernández, J. M. J., González-Santiago, O., Ramírez-Cabrera, M. A., Esquivel-Ferriño, P. C., & Camacho-Corona, M. D. R. (2016). Chemistry and pharmacology of *Citrus sinensis. Molecules (Basel, Switzerland)*, *21*(2), 247. doi:10.3390/molecules21020247

Fialová, S., Tekel'ová, D., Mrlianová, M., & Grančai, D. (2008). The determination of phenolics compounds and antioxidant activity of mints and balms cultivated in Slovakia. *Acta Facultatis Pharmaceuticae Universitatis Comenianae*, *55*, 96–102.

Fiore, C., Eisenhut, M., Ragazzi, E., Zanchin, G., & Armanini, D. (2005). A history of the therapeutic use of liquorice in Europe. *Journal of Ethnopharmacology*, *99*(3), 317–324. doi:10.1016/j.jep.2005.04.015 PMID:15978760

Fischer, R., Stoger, E., Schillberg, S., Christou, P., & Twyman, R. M. (2004). Plant-based production of biopharmaceuticals. *Current Opinion in Plant Biology*, *7*(2), 152–158. doi:10.1016/j.pbi.2004.01.007 PMID:15003215

Flora of China. (n.d.). *Eupatorium cannabinum*. Error! Hyperlink reference not valid..aspx?flora_id=2&taxon_id=200023930

Foyer, C. H., & Noctor, G. (2005). Redox homeostasis and antioxidant signaling: A metabolic interface between stress perception and physiological responses. *The Plant Cell*, *17*(7), 1866–1875. doi:10.1105/tpc.105.033589 PMID:15987996

Fozdar, N. G., Bauadia, V. N., & Vahia, N. S. (1962). Preliminary Report Of An Indigenous Drug" *Acorus calamus*" In Psychiatric Disorders. *Indian Journal of Psychiatry*, *4*(1), 12.

Fraisse, D., Felgines, C., Texier, O., & Lamaison, J. L. (2011). Caffeoyl derivatives: Major antioxidant compounds of some wild herbs of the Asteraceae family. *Food and Nutrition Sciences*, *2*(03), 181–192. doi:10.4236/fns.2011.230025

Freese, J. L., Pino, D., & Pleasure, S. J. (2010). Wnt signaling in development and disease. *Neurobiology of Disease*, *38*(2), 148–153. doi:10.1016/j.nbd.2009.09.003 PMID:19765659

Fresco, P., Borges, F., Diniz, C., & Marques, M. P. M. (2006). New insights on the anticancer properties of dietary polyphenols. *Medicinal Research Reviews*, *26*(6), 747–766. doi:10.1002/med.20060 PMID:16710860

Fujiwara, H., Iwasaki, K., Furukawa, K., Seki, T., He, M., Maruyama, M., & Saido, T. C. (2006). *Uncaria rhynchophylla*, a Chinese medicinal herb, has potent antiaggregation effects on Alzheimer's β-amyloid proteins. *Journal of Neuroscience Research*, *84*(2), 427–433. doi:10.1002/jnr.20891 PMID:16676329

Fujiwara, H., Tabuchi, M., Yamaguchi, T., Iwasaki, K., Furukawa, K., Sekiguchi, K., & Saido, T. C. (2009). A traditional medicinal herb *Paeonia suffruticosa* and its active constituent 1, 2, 3, 4, 6-penta-O-galloyl-β-d-glucopyranose have potent anti-aggregation effects on Alzheimer's amyloid β proteins in vitro and in vivo. *Journal of Neurochemistry*, *109*(6), 1648–1657. doi:10.1111/j.1471-4159.2009.06069.x PMID:19457098

Fukuoka, T., Ohya, S., Narita, T., Katsuta, M., Iijima, M., Masuda, N., ... Nikaido, H. (1993). Activity of the carbapenem panipenem and role of the OprD (D2) protein in its diffusion through the *Pseudomonas aeruginosa* outer membrane. *Antimicrobial Agents and Chemotherapy*, *37*(2), 322–327. doi:10.1128/AAC.37.2.322 PMID:8452364

Fu, P., Lin, S., Shan, L., Lu, M., Shen, Y. H., Tang, J., ... Zhang, W. D. (2009). Constituents of the moss *Polytrichum commune*. *Journal of Natural Products*, *72*(7), 1335–1337. doi:10.1021/np800830v PMID:19572610

Gabriëlla, H.S. & Ameenah, G.F. (2013). *Medicinal Plants Plant Resources of Tropical Africa (Program)*. Academic Press.

Galbraith, D. W. (2007). Nanobiotechnology: Silica breaks through in plants. *Nature Nanotechnology*, *2*(5), 272–273. doi:10.1038/nnano.2007.118 PMID:18654282

Ganeshkumar, M., Ponrasu, T., Krithika, R., Iyappan, K., Gayathri, V. S., & Suguna, L. (2012). Topical application of *Acalypha indica* accelerates rat cutaneous wound healing by up-regulating the expression of Type I and III collagen. *Journal of Ethnopharmacology*, *142*(1), 14–22. doi:10.1016/j.jep.2012.04.005 PMID:22521732

Ganguly, S., Saha, P., Chatterjee, M., & Maji, A. K. (2014). Prevalence of polymorphisms in antifolate drug resistance molecular marker genes pvdhfr and pvdhps in clinical isolates of *Plasmodium vivax* from Kolkata, India. *Antimicrobial Agents and Chemotherapy*, *58*(1), 196–200. doi:10.1128/AAC.01171-13 PMID:24145518

Ganjre, A., Kathariya, R., Bagul, N., & Pawar, V. (2015). Anti-carcinogenic and antibacterial properties of selected spices: Implications in Oral Health. *Clinical Nutrition Research*, *4*(4), 209–215. doi:10.7762/cnr.2015.4.4.209 PMID:26566515

Gao, L., Cai, G., & Shi, X. (2008). β-Ecdysterone induces osteogenic differentiation in mouse mesenchymal stem cells and relieves osteoporosis. *Biological & Pharmaceutical Bulletin*, *31*(12), 2245–2249. doi:10.1248/bpb.31.2245 PMID:19043207

Garba, A., Mada, S. B., Ibrahim, G., Dauran, I. A., & Hamza, A. B. (2013). *Studies on hypoglycemic and hypolipidemic effects of methanolic extract of Stachytarpheta angustifolia (mill) in streptozotoin induced diabetic rats*. *Asian J. Bio. Sci*. doi:10.3923/ajbs.2013

Garcia, L. S. (2010). Malaria. *Clinics in Laboratory Medicine*, *30*(1), 93–129. doi:10.1016/j.cll.2009.10.001 PMID:20513543

Garg, P., & Grewal, A. (2015). In vitro antibacterial activity of *Ageratum conyzoides* L. *World Journal of Pharmacy and Pharmaceutical Sciences*, *4*(7), 893–897.

Garg, V. K., & Paliwal, S. K. (2011). Wound-healing activity of ethanolic and aqueous extracts of *Ficus benghalensis. Journal of Advanced Pharmaceutical Technology & Research*, *2*(2), 110–114. doi:10.4103/2231-4040.82957 PMID:22171302

Gaur, K., Kori, M. L., & Nema, R. K. (2009). Comparative screening of immunomodulatory activity of hydro-alcoholic extract of *Hibiscus rosa sinensis* Linn. and ethanolic extract of Cleome gynandra Linn. *Global Journal of Pharmacology*, *3*(2), 85–89.

Gautam, A., Jhade, D., Ahirwar, D., Sujane, M., & Sharma, G. N. (2010). Pharmacognostic evaluation of Toona ciliata bark. *Journal of Advanced Pharmaceutical Technology & Research*, *1*, 216–220. PMID:22247848

Gayathri, M., & Kannabiran, K. (2009). Antimicrobial activity of *Hemidesmus indicus, Ficus bengalensis* and *Pterocarpus marsupium* roxb. *Indian Journal of Pharmaceutical Sciences*, *71*(5), 578–581. doi:10.4103/0250-474X.58182 PMID:20502584

Gebreyohannes, G., & Gebreyohannes, M. (2013). Medicinal values of garlic: A review. *International Journal of Medical Sciences*, *5*(9), 401–408.

George, S. A., George, M., Joseph, L., & James, E. (2019). A Review on antiulcer, antidiabetic and hepatoprotective activity of *Ocimum sanctum* and *Musa paradisiacaInt. J. Pharm & Pharmaceu Res*. *Human Journals*, *15*(2), 70–76.

Gerhardt, H., Seifert, F., Buvari, P., Vogelsang, H., & Repges, R. (2001). Therapy of active Crohn's disease with *Boswellia serrata* extract H 15. *Zeitschrift fur Gastroenterologie*, *39*(1), 11–17. doi:10.1055-2001-10708 PMID:11215357

Gerlach, U., & Hiby, W. (1974). Sorbitol dehydrogenase. In *Methods of enzymatic analysis* (pp. 569–573). Academic Press. doi:10.1016/B978-0-12-091302-2.50008-6

Gérrard, E. J. P., Peter, C., Xuan, L., & Derek, F. (2013). Green biosynthesis of gold nanometre scale plates using the leaf extracts from an indigenous Australian plant *Eucalyptus macrocarpa. Gold Bulletin*, *46*(3), 165–173. doi:10.100713404-013-0096-7

Ghani, A. (2003). *Medicinal plants of Bangladesh: Chemical constituents and uses* (2nd ed.). Dhaka, Bangladesh: The Asiatic Society of Bangladesh.

Ghasi, S., Nwobodo, E., & Ofili, J. O. (2000). Hypocholesterolemic effects of crude extract of leaf of *Moringa oleifera* Lam in high-fat diet fed wistar rats. *Journal of Ethnopharmacology*, *69*(1), 21–25. doi:10.1016/S0378-8741(99)00106-3 PMID:10661880

Ghate, N. B., Hazra, B., Sarkar, R., & Mandal, N. (2014). Heartwood extract of *Acacia catechu* induces apoptosis in human breast carcinoma by altering bax/bcl-2 ratio. *Pharmacognosy Magazine*, *10*(37), 27–33. doi:10.4103/0973-1296.126654 PMID:24695415

Ghazali, N. A., Elmy, A., Yuen, L. C., Sani, N. Z., Das, S., Suhaimi, F., & Thent, Z. C. (2016). *Piper betel* leaves induces wound healing activity via proliferation of fibroblasts and reducing 11β hydroxysteriod dehydrogenase-1 expression in diabetic rat. *Journal of Ayurveda and Integrative Medicine*, *7*(4), 198–208. doi:10.1016/j.jaim.2016.08.008 PMID:27889427

Ghosh, S., Banerjee, S., & Sil, P. C. (2015). The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. *Food and Chemical Toxicology*, *83*, 111–124. doi:10.1016/j.fct.2015.05.022 PMID:26066364

Ghritlahare, S. K., Satapathy, T., Panda, P. K., & Mishra, G. (2017). Ethnopharmacological Story of Guggul Sterones: An Overview. *Research Journal of Pharmacognosy and Phytochemistry*, *9*(3), 182–188. doi:10.5958/0975-4385.2017.00034.6

Giedraitiene, A., & Vitkauskien, ˙. E. (2011). Antibiotic resistance mechanisms of clinically important bacteria. *Medicina*, *47*(3), 137–146. doi:10.3390/medicina47030019 PMID:21822035

Gill, S. S., & Tuteja, N. (2010). Reactive oxygen species and antioxidant machinery in abiotic stress tolerance in crop plants. *Plant Physiology and Biochemistry*, *48*(12), 909–930. doi:10.1016/j.plaphy.2010.08.016 PMID:20870416

Ginghina, C., Bejan, I., & Ceck, C. D. (2011). Modern risk stratification in coronary heart disease. *Journal of Medicine and Life*, *4*(4), 377–386. PMID:22514570

Giorgi, A., De Marinis, P., Granelli, G., Chiesa, L. M., & Panseri, S. (2013). Secondary metabolite profile, antioxidant capacity, and mosquito repellent activity of *Bixa orellana* from Brazilian Amazon region. *Journal of Chemistry*. *Article ID*, *409826*, 1–10.

Gitzinger, M., Parsons, J., Reski, R., & Fussenegger, M. (2009). Functional cross-kingdom conservation of mammalian and moss (*Physcomitrella patens*) transcription, translation and secretion machineries. *Plant Biotechnology Journal*, *7*(1), 73–86. doi:10.1111/j.1467-7652.2008.00376.x PMID:19021876

Glime, J. M. (2007). Economic and ethnic uses of bryophytes. *Flora of North America*, *27*, 14–41.

Goel, H. L., & Mercurio, A. M. (2013). VEGF targets the tumor cell. *Nature Reviews. Cancer*, *13*(12), 871–882. doi:10.1038/nrc3627 PMID:24263190

Gogoi, B., & Zaman, K. (2013). Phytochemical constituents of some medicinal plant species used in recipe during 'Bohag Bihu' in Assam. *Journal of Pharmacognosy and Phytochemistry*, *2*(2), 30–40.

Gogoi, J., Nakhuru, K. S., Chattophadhayay, P., Rai, A. K., Gogoi, H. K., & Veer, V. (2013). In vivo evaluation of cutaneous wound healing activity of *Mirabilis jalapa* L radix. *Oriental Pharmacy and Experimental Medicine*, *14*(2), 103–109. doi:10.100713596-013-0122-6

Gómez-García, M. D. R., & Ochoa-Alejo, N. (2013). Biochemistry and molecular biology of carotenoid biosynthesis in chili peppers (*Capsicum* spp.). *International Journal of Molecular Sciences*.

Gopalakrishna, C. H., Reddy, A. K., Sharief, N., Sushma, K. R., & Narendra, S. (2014). A study on anti-ulcer activity of *Diospyros malabarica* bark in ulcer induced rats. *International Journal for Pharmaceutical Research Scholars*, *3*(2), 375–381.

Gorzalczany, S., Muschietti, L., Repetto, M., & Kartin, L. (2008). Chloretic and antioxidant effect of *Eupatorium buniifolium. Pharmacologyonline*, *1*, 139–147.

Grana, S. G., Ameneira, M. P., Vecino, X., Santos, I. P., Juste, J. P., Cruz, J. M., & Moldes, A. B. (2017). Biogenic synthesis of metal nanoparticles using a biosurfactant extracted from corn and their antimicrobial properties. *Nanomaterials (Basel, Switzerland)*, *7*(6), 139–152. doi:10.3390/nano7060139 PMID:28587297

Greenish, H. G. (1920). *A Text Book of Materia Medica: Being an Account of the More Important Crude Drugs of Vegetable and Animal Origin*. J. & A. Churchill.

Gregory, M., Divya, B., Mary, R. A., Viji, M. H., Kalaichelvan, V. K., & Palanivel, V. (2013). Anti–ulcer activity of *Ficus religiosa* leaf ethanolic extract. *Asian Pacific Journal of Tropical Biomedicine*, *3*(7), 554–556. doi:10.1016/S2221-1691(13)60112-4 PMID:23836366

Gu, H., Ho, P. L., Edmond, T., Ling, W., & Xu, B. (2003). Presenting vancomycin on nanoparticles to enhance antimicrobial activities. *Nano Letters*, *3*(9), 1261–1263. doi:10.1021/nl034396z

Gülçin, I. (2010). Antioxidant properties of resveratrol: A structure–activity insight. *Innovative Food Science & Emerging Technologies*, *11*(1), 210–218. doi:10.1016/j.ifset.2009.07.002

Guo, Y., & Pei, X. (2019). Tetrandrine-induced autophagy in MDA-MB-231 triple-negative breast cancer cell through the inhibition of PI3K/AKT/mTOR signalling. *Evidence-Based Complementary and Alternative Medicine*, *2019*, 1–11. doi:10.1155/2019/7517431 PMID:30713576

Gupta, A., Karchuli, M., & Upmanyu, N. (2013). Comparative evaluation of ethanolic extracts of Bacopa monnieri, Evolvulus alsinoides, *Tinospora cordifolia* and their combinations on cognitive functions in rats. *Current Aging Science*, *6*(3), 239–243. doi:10.2174/1874609811205999003 6 PMID:23866011

Gupta, G. D., Sujatha, N., Dhanik, A., & Rai, N. P. (2010). Clinical evaluation of Shilajatu Rasayana in patients with HIV infection. *Ayurveda*, *31*(1), 28–32. doi:10.4103/0974-8520.68205 PMID:22131681

Gupta, I., Gupta, V., Parihar, A., Gupta, S., Lüdtke, R., Safayhi, H., & Ammon, H. P. (1998). Effects of *Boswellia serrata* gum resin in patients with bronchial asthma: Results of a double-blind, placebo-controlled, 6-week clinical study. *European Journal of Medical Research*, *3*(11), 511–514. PMID:9810030

Gupta, I., Parihar, A., Malhotra, P., Singh, G. B., Lüdtke, R., Safayhi, H., & Ammon, H. P. (1997). Effects of *Boswellia serrata* gum resin in patients with ulcerative colitis. *European Journal of Medical Research*, *2*(1), 37–43. PMID:9049593

Gupta, R. S., & Sharma, A. (2003). Antifertility effect of *Tinospora cordifolia* (Willd.) stem extract in male rats. *Indian Journal of Experimental Biology*, *41*, 885–889. PMID:15248490

Gupta, R., & Sharma, V. (2011). Ameliorative effects of *Tinospora cordifolia* root extract on histopathological and biochemical changes induced by aflatoxin-B1 in mice kidney. *Toxicology International*, *18*(2), 94. doi:10.4103/0971-6580.84259 PMID:21976812

Gupta, S., Mediratta, P. K., Singh, S., Sharma, K. K., & Shukla, R. (2006). Antidiabetic, antihypercholesterolaemic and antioxidant effect of *Ocimum sanctum* (Linn) seed oil. *Indian Journal of Experimental Biology*, *44*(4), 300–304. PMID:16629372

Gupta, S., & Prakash, J. (2009). Studies on Indian green leafy vegetables for their antioxidant activity. *Plant Foods for Human Nutrition (Dordrecht, Netherlands)*, *64*(1), 39–45. doi:10.1007/11130-008-0096-6 PMID:18985454

Gurib-Fakim, A. (2006). Medicinal plants: Tradition of yesterday and drugs of tomorrow. Review article. *Molecular Aspects of Medicine*, *27*(1), 1–93. doi:10.1016/j.mam.2005.07.008 PMID:16105678

Gushiken, L. F., Beserra, F. P., Rozza, A. L., Bérgamo, P. L., Bérgamo, D. A., & Pellizzon, C. H. (2016). Chemical and biological aspects of extracts from medicinal plants with antidiabetic effects. *The Review of Diabetic Studies; RDS*, *13*(2-3), 96–112. doi:10.1900/RDS.2016.13.96 PMID:28012277

Gutteridge, J. M. C., & Halliwell, B. (2010). Antioxidants: Molecules, medicines and myths. *Biochemical and Biophysical Research Communications*, *393*(4), 561–564. doi:10.1016/j.bbrc.2010.02.071 PMID:20171167

Hajhashemi, V., & Abbasi, N. (2008). Hypolipidemic activity of *Anethum graveolens* in rats. Phytotherapy Research. *An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *22*(3), 372–375. PMID:18058989

Halder, P. K., Paul, N., & Beg, M. R. A. (2014). Prospect of *Pongamia pinnata* (Karanja) in Bangladesh: A sustainable source of liquid fuel. *Journal of Renewable Energy*, *2014*, 1–13. doi:10.1155/2014/647324

Halliwell, B. (2007). Flavonoids: A re-run of the carotenoids story. *Novartis Foundation Symposium*, *282*, 93–104. doi:10.1002/9780470319444.ch7 PMID:17913226

Halsey, R.W. & Keeley, J.E. (2016). *Conservation Issues: California Chaparral*. Academic Press.

Hamidpour, R., Hamidpour, S., Hamidpour, M., & Shahlari, M. (2013). Frankincense (*Boswellia* species): From the selection of traditional applications to the novel phytotherapy for the prevention and treatment of serious diseases. *Journal of Traditional and Complementary Medicine*, *3*(4), 221. doi:10.4103/2225-4110.119723 PMID:24716181

Han, A., & Mirmirani, P. (2006). *Clinical approach to the patient with alopecia*. Academic Press.

Hariharan, N., & Rao, T. S. (2019). The evolving role of pathologic complete response in breast cancer. *South Asian Journal of Cancer*, *8*(4), 210. doi:10.4103ajc.sajc_67_19 PMID:31807476

Hasanpourghadi, M., Pandurangan, A. K., & Mustafa, M. R. (2018). Modulation of oncogenic transcription factors by bioactive natural products in breast cancer. *Pharmacological Research*, *128*, 376–388. doi:10.1016/j.phrs.2017.09.009 PMID:28923544

Hashimoto, K., Katsuhara, T., Itoh, H., Ikeya, Y., Okada, M., & Mitsuhashi, H. (1990). Monoterpenes from asiasari radix from *Asiasarum* sp. *Phytochemistry*, *29*(11), 3571–3574. doi:10.1016/0031-9422(90)85278-N

Hayat, M. Q., Khan, M. A., Ashraf, M., & Jabeen, S. (2009). Ethnobotany of the genus *Artemisia*, L. (Asteraceae) in Pakistan. *Ethnobotany Research and Applications*, *7*, 147–162. doi:10.17348/era.7.0.147-162

Hay, I. C., Jamieson, M., & Ormerod, A. D. (1998). Randomized trial of aromatherapy: Successful treatment for alopecia areata. *Archives of Dermatology*, *134*(11), 1349–1352. doi:10.1001/archderm.134.11.1349 PMID:9828867

Hendriks, H., Balraadjsing, W., Huizing, H. J., & Bruins, A. P. (1987). Investigation into the presence of pyrrolizidine alkaloids in *Eupatorium cannabinum* by means of positive and negative ion chemical ionization GC-MS. *Planta Medica*, *53*(5), 456–461. doi:10.1055-2006-962772 PMID:17269067

Hendriks, H., Malingré, T. M., & Elema, E. T. (1983). Pyrrolizidine alkaloids, flavonoids and volatile compounds in the genus Eupatorium. *Eupatorium cannabinum* L., an ancient drug with new perspectives. *Pharmaceutisch Weekblad. Scientific Edition*, *5*(6), 281–286. doi:10.1007/BF02074855 PMID:6364036

Herculano, E. D., da Costa, C., Rodriques, A. K., Araújo-Júnior, J. X., Santana, E. G., França, P. H., ... Ribeiro, Ê. A. (2014). Evaluation of cardiovascular effects of edible fruits of *Syzygium cumini* Myrtaceae (L) Skeels in rats. *Tropical Journal of Pharmaceutical Research*, *13*(11), 1853–1861. doi:10.4314/tjpr.v13i11.12

Herodež, Š. S., Hadolin, M. Š., Škerget, M., & Knez, Ž. (2003). Solvent extraction study of antioxidants from balm. *Food Chemistry*, *80*(2), 275–282. doi:10.1016/S0308-8146(02)00382-5

He, X., Fang, J., Huang, L., Wang, J., & Huang, X. (2015). *Sophora flavescens* Ait.: Traditional usage, phytochemistry and pharmacology of an important traditional Chinese medicine. *Journal of Ethnopharmacology*, *172*, 10–29. doi:10.1016/j.jep.2015.06.010 PMID:26087234

Hirsch, E. C., & Hunot, S. (2009). Neuroinflammation in Parkinson's disease: A target for neuroprotection? *Lancet Neurology*, *8*(4), 382–397. doi:10.1016/S1474-4422(09)70062-6 PMID:19296921

Hoareau, L., & DaSilva, E. J. (1999). Medicinal plants: A re-emerging health aid. *Electronic Journal of Biotechnology*, *2*(2), 3–4.

Høiby, N., Bjarnsholt, T., Givskov, M., Molin, S., & Ciofu, O. (2010). Antibiotic resistance of bacterial biofilms. *International Journal of Antimicrobial Agents*, *35*(4), 322–332. doi:10.1016/j.ijantimicag.2009.12.011 PMID:20149602

Hojo, H., & Sato, J. (2002). Antifungal activity of Licorice (*Glycyrrhiza glabra)* and potential applications in beverage foods. *J Food Ingr Japan*, *203*, 45–49.

Hollman, P. C., & Arts, I. C. (2000). Flavonols, flavones and flavanols - Nature, occurrence and dietary burden. *Journal of the Science of Food and Agriculture*.

Hollman, P. C. H., & Katan, M. B. (1999). Dietary flavonoids: Intake, health effects and bioavailability. *Food and Chemical Toxicology*, *37*(9-10), 937–942. doi:10.1016/S0278-6915(99)00079-4 PMID:10541448

Holtz, C. (2007). *Global health care: Issues and policies*. Sudbury, MA: Jones & Barlett Publishers.

Holtz, C. (2007). *Global Health Care: Issues and Policies*. Sudbury, MA: Jones & Barlett Publishers.

Hosseini, M., Hadjzadeh, M. A. R., Derakhshan, M., Havakhah, S., Rassouli, F. B., Rakhshandeh, H., & Saffarzadeh, F. (2010). The beneficial effects of olibanum on memory deficit induced by hypothyroidism in adult rats tested in Morris water maze. *Archives of Pharmacal Research*, *33*(3), 463–468. doi:10.100712272-010-0317-z PMID:20361313

Houghton, P. J., & Howes, M.-J. (2005). Natural products and derivatives affecting neurotransmission relevant to Alzheimer's and Parkinson's disease. *Neuro-Signals*, *14*(1-2), 6–22. doi:10.1159/000085382 PMID:15956811

Hou, X., Rivers, J., León, P., McQuinn, R. P., & Pogson, B. J. (2016). Synthesis and function of apocarotenoid Ssgnals in plants. *Trends in Plant Science*, *21*(9), 792–803. doi:10.1016/j.tplants.2016.06.001 PMID:27344539

Hou, Y.-C., Chao, P.-D. L., & Chen, S.-Y. (2000). Honokiol and magnolol increased hippocampal acetylcholine release in freely-moving rats. *The American Journal of Chinese Medicine*, *28*(3-4), 379–384. doi:10.1142/S0192415X00000441 PMID:11154051

Howes, M. J. R., & Houghton, P. (2003). Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function. *Pharmacology, Biochemistry, and Behavior*, *75*(3), 513–527. doi:10.1016/S0091-3057(03)00128-X PMID:12895669

Ho, Y.-S., Yu, M.-S., Yang, X.-F., So, K.-F., Yuen, W.-H., & Chang, R. C.-C. (2010). Neuroprotective effects of polysaccharides from wolfberry, the fruits of *Lycium barbarum*, against homocysteine-induced toxicity in rat cortical neurons. *Journal of Alzheimer's Disease*, *19*(3), 813–827. doi:10.3233/JAD-2010-1280 PMID:20157238

Hsieh, C.-L., Ho, T.-Y., Su, S.-Y., Lo, W.-Y., Liu, C.-H., & Tang, N.-Y. (2009). *Uncaria rhynchophylla* and rhynchophylline inhibit c-Jun N-terminal kinase phosphorylation and nuclear factor-κB activity in kainic acid-treated rats. *The American Journal of Chinese Medicine*, *37*(2), 351–360. doi:10.1142/S0192415X09006898 PMID:19507277

Huang, G. C., Chow, J. M., Shen, S. C., Yang, L. Y., Lin, C. W., & Chen, Y. C. (2007). Wogonin but not Nor-wogonin inhibits lipopolysaccharide and lipoteichoic acid-induced iNOS gene expression and NO production in macrophages. *International Immunopharmacology*, *7*(8), 1054–1063. doi:10.1016/j.intimp.2007.04.001 PMID:17570322

Huang, K. C. (1993). *Yan Hu Suo–the dried tuber of Corydalis turtschaninovii Bess f. yanhusu (Papaveraceae). The Pharmacology of Chinese Herbs*. Boca Raton, FL: CRC Press.

Huang, K. C. (1998). *The pharmacology of Chinese herbs*. Routledge.

Huang, W. C., Gu, P. Y., Fang, L. W., Huang, Y. L., Lin, C. F., & Liou, C. J. (2019). Sophoraflavanone G from *Sophora flavescens* induces apoptosis in triple-negative breast cancer cells. *Phytomedicine*, *61*, 152852. doi:10.1016/j.phymed.2019.152852 PMID:31035052

Huang, W. C., Tsai, P. J., & Chen, Y. C. (2007). Functional gold nanoparticles as photothermal agents for selective-killing of pathogenic bacteria. *Nanomed.*, *2*(6), 777–787. doi:10.2217/17435889.2.6.777 PMID:18095845

Huang, W. Y., Cai, Y.-Z., Xing, J., Corke, H., & Sun, M. (2008). Comparative analysis of bioactivities of four *Polygonum* species. *Planta Medica*, *74*(1), 43–49. doi:10.1055-2007-993759 PMID:18067063

Hu, C., & Kitts, D. D. (2003). Antioxidant, pro-oxidant and cytotoxic activities of solvent fractionated dandelion (*Taraxacum officinale*) flower extracts in vitro. *Journal of Agricultural and Food Chemistry*, *51*(1), 301–310. doi:10.1021/jf0258858 PMID:12502425

Huh, Y. S., Hong, T. H., & Hong, W. H. (2004). Effective extraction of oligomeric proanthocyanidin (OPC) from wild grape seeds. *Biotechnology and Bioprocess Engineering; BBE*, *9*(6), 471–475. doi:10.1007/BF02933488

Hui, K. M., Huen, M. S., Wang, H. Y., Zheng, H., Sigel, E., Baur, R., ... Xue, H. (2002). Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from *Scutellaria baicalensis* Georgi. *Biochemical Pharmacology*, *64*(9), 1415–1424. doi:10.1016/S0006-2952(02)01347-3 PMID:12392823

Hulkiere, M. M., Joshi, C. G., Ananda, D., Poyya, J., Kudva, A. K., & Dhananjaya, B. L. (2017). Biogenic synthesis of gold nanoparticles by marine endophytic fungus-*Cladosporium cladosporioides* isolated from seaweed and evaluation of their antioxidant and antimicrobial properties. *Process Biochemistry*, *63*, 137–144. doi:10.1016/j.procbio.2017.09.008

Humphreys, D. P., & Glover, D. J. (2001). Therapeutic antibody production technologies: Molecules, applications, expression, and purification. *Current Opinion in Drug Discovery & Development*, *4*(2), 172–185. PMID:11378956

Hurwitz, E. S., Johnson, D., & Campbell, C. C. (1981). Resistance of *Plasmodium falciparum* malaria to sulfadoxine-pyrimethamine ('Fansidar') in a refugee camp in Thailand. *Lancet*, *1*(8229), 1068–1070. doi:10.1016/S0140-6736(81)92239-X PMID:6112445

Husen, A., & Siddiqi, K. S. (2014). Phytosynthesis of nanoparticles: Concept, controversy and application. *Nanoscale Research Letters*, *9*(1), 229–252. doi:10.1186/1556-276X-9-229 PMID:24910577

Hussain, A. I., Rathore, H. A., Sattar, M. Z. A., Chatha, S. A. S., Sarker, S. D., & Gilani, A. H. (2014). *Citrullus colocynthis* (L.) Schrad (bitter apple fruit): A review of its phytochemistry, pharmacology, traditional uses and nutritional potential. *Journal of Ethnopharmacology*, *155*(1), 54–66. doi:10.1016/j.jep.2014.06.011 PMID:24936768

Hussain, M., & Gorsi, M. (2004). Antimicrobial activity of *Nerium oleander* Linn. *Asian J. Plant Sci.*, *3*(2), 177–180. doi:10.3923/ajps.2004.177.180

Hussain, S. M., Hess, K. L., Gearhart, J. M., Geiss, K. T., & Schlager, J. J. (2005). In vitro toxicity of nanoparticles in BRL 3A rat liver cells. *Toxicology In Vitro*, *19*(7), 975–983. doi:10.1016/j.tiv.2005.06.034 PMID:16125895

Hwang, B. Y., Roberts, S. K., Chadwick, L., Wu, C. D., & Kinghorn, D. A. (2003). Antimicrobial constitutents from goldenseal (the rhizomes of *Hydrastis canadensis*) against selected oral pathogens. *Planta Medica*, *69*(7), 623–627. doi:10.1055-2003-41115 PMID:12898417

Ibrahim, H. M. M. (2015). Green synthesis and characterization of silver nanoparticles using banana peel extract and their antimicrobial activity against representative microorganisms. J. Radiat. *Res. Appl. Sci.*, *8*, 265–275.

Ighodaro, O. M., & Akinloye, O. A. (2018). First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria Journal of Medicine*, *54*(4), 287–293. doi:10.1016/j.ajme.2017.09.001

Igwe, C. U., Ojiako, O. A., Nwaogu, L. A., & Onyeze, G. O. C. (2008). Lipid lowering effect of aqueous leaf extract of *Spondias mombin* Linn. *Journal de Pharmacologie*, *6*(1), 10.

Imaida, K., Fukushima, S., Shirai, T., Ohtani, M., Nakanishi, K., & Ito, N. (1983). Promoting activities of butylated hydroxyanisole and butylated hydroxytoluene on 2-stage urinary bladder carcinogenesis and inhibition of γ-glutamyl transpeptidase-positive foci development in the liver of rats. *Carcinogenesis*, *4*(7), 895–899. doi:10.1093/carcin/4.7.895 PMID:6135514

Imenshahidi, M., & Hosseinzadeh, H. (2016). *Berberis vulgaris* and berberine: An update review. *Phytotherapy Research*, *30*(11), 1745–1764. doi:10.1002/ptr.5693 PMID:27528198

Imperato, P. J. (1981). Modern and traditional medicine: The case of Mali. *Annals of Internal Medicine*, *95*(5), 650–651. doi:10.7326/0003-4819-95-5-650 PMID:7294557

Imtiaz, F., Islam, M., Saeed, H., Saleem, B., Asghar, M., & Saleem, Z. (2017). Impact of *Trigonella foenum-graecum* Leaves Extract on Mice Hair Growth. *Pakistan Journal of Zoology*, *49*(4), 1405–1412. doi:10.17582/journal.pjz/2017.49.4.1405.1412

Imwong, M., Pukrittayakamee, S., Renia, L., Letourneur, F., Charlieu, J. P., Leartsakulpanich, U., ... Snounou, G. (2003). Novel point mutations in the dihydrofolate reductase gene of *Plasmodium vivax*: Evidence for sequential selection by drug pressure. *Antimicrobial Agents and Chemotherapy*, *47*(5), 1514–1521. doi:10.1128/AAC.47.5.1514-1521.2003 PMID:12709316

Indran, M., Mahmood, A. A., & Kuppusamy, U. R. (2008). Protective effect of *Carica papaya* L leaf extract against alcohol induced acute gastric damage and blood oxidative stress in rats. *The West Indian Medical Journal*, *57*(4), 323–326. PMID:19566009

Inoue-Choi, M., Sinha, R., Gierach, G. L., & Ward, M. H. (2016). Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP diet and health study. *International Journal of Cancer*, *138*(7), 1609–1618. doi:10.1002/ijc.29901 PMID:26505173

Ionita, L., Grigore, A., Pirvu, L., Draghici, E., Bubueanu, C., Ionita, C., ... Dobre, N. (2013). Pharmacological activity of a *Eupatorium cannabinum* L. extract. *Romanian Biotechnological Letters*, *18*(6), 8779–8786.

Iriti, M., Faoro, F., Iriti, M., & Faoro, F. (2009). Chemical diversity and defence metabolism: How plants cope with pathogens and ozone pollution. *International Journal of Molecular Sciences*, *10*(8), 3371–3399. doi:10.3390/ijms10083371 PMID:20111684

Irwin, R. L., & Smith Iii, H. J. (1960). Cholinesterase inhibition by galanthamine and lycoramine. *Biochemical Pharmacology*, *3*(2), 147–148. doi:10.1016/0006-2952(60)90030-7 PMID:13853036

Ishaq, M. S., Hussain, M. M., Siddique Afridi, M., Ali, G., Khattak, M., & Ahmad, S. (2014). *In vitro* phytochemical, antibacterial, and antifungal activities of leaf, stem, and root extracts of *Adiantum capillus veneris. TheScientificWorldJournal*, *269793*. doi:10.1155/2014/269793 PMID:24592156

Ishida, H., Inaoka, Y., Okada, M., Fukushima, M., Fukazawa, H., & Tsuji, K. (1999). Studies of the Active Substances in Herbs Used for Hair Treatment. III. Isolation of Hair-Regrowth Substances from *Polygara senega* var. *latifolia* Torr. (Gray). *Biological & Pharmaceutical Bulletin*, *22*(11), 1249–1250. doi:10.1248/bpb.22.1249 PMID:10598039

ITIS. (n.d.). *Eupatorium cannabinuz*. https://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN& search _ value =35984

Ivan, A. R. (2006). *Medicinal Plant of World: Chemical Constituents*. Traditional Uses and Modern Medicinal Uses, Human Press Totowa.

Jabeen, K., & Javaid, A. (2010). Antifungal activity of *Syzygium cumini* against *Ascochyta rabiei*–the cause of chickpea blight. *Natural Product Research*, *24*(12), 1158–1167. doi:10.1080/14786410902941154 PMID:19588279

Jabeen, R., Ahmad, A., & Iqbal, M. (2009). Phytoremediation of heavy metals: Physiological and molecular aspects. *Botanical Review*, *75*(4), 339–364. doi:10.100712229-009-9036-x

Jagetia, G. C., Nayak, V., & Vidyasagar, M. S. (1998). Evaluation of the antineoplastic activity of guduchi (*Tinospora cordifolia*) in cultured HeLa cells. *Cancer Letters*, *127*(1), 71–82. doi:10.1016/S0304-3835(98)00047-0 PMID:9619860

Jagetia, G. C., & Rao, S. K. (2006). Evaluation of the antineoplastic activity of guduchi (*Tinospora cordifolia*) in Ehrlich ascites carcinoma bearing mice. *Biological & Pharmaceutical Bulletin*, *29*(3), 460–466. doi:10.1248/bpb.29.460 PMID:16508146

Jahan, R., Al-Nahain, A., Majumder, S., & Rahmatullah, M. (2014). Ethnopharmacological significance of *Eclipta alba* (L.) hassk. (Asteraceae). *International Scholarly Research Notices*, 2014. PMID:27355071

Jain, N., Jain, R., Jain, A., Jain, D. K., & Chandel, H. S. (2010). Evaluation of wound-healing activity of *Acorus calamus* Linn. *Natural Product Research*, *24*(6), 534–541. doi:10.1080/14786410802531782 PMID:20182947

Jain, P. K., Das, D., Pandey, N., & Jain, P. (2016). Traditional Indian herb *Emblica officinalis* and its medicinal importance. *Innov J Ayurvedic Sci*, *4*(4), 1–15.

Jain, V., Basak, S., Bhandari, S., Bharti, P. K., Thomas, T., Singh, M. P., & Singh, N. (2014). Burden of complicated malaria in a densely forested Bastar region of Chhattisgarh State (central India). *PLoS One*, *9*(12), 115–266. doi:10.1371/journal.pone.0115266 PMID:25531373

Jalsrai, A., Numakawa, T., Kunugi, H., Dieterich, D. C., & Becker, A. (2016). The neuroprotective effects and possible mechanism of action of a methanol extract from *Asparagus cochinchinensis: In vitro* and *in vivo* studies. *Neuroscience*, *322*, 452–463. doi:10.1016/j.neuroscience.2016.02.065 PMID:26947129

Jamir, T. T., Sharma, H. K., & Dolui, A. K. (1999). Folklore medicinal plants of Nagaland, India. *Fitoterapia*, *70*(4), 395–401. doi:10.1016/S0367-326X(99)00063-5

Janbaz, K. H., Zaeem Ahsan, M., Saqib, F., Imran, I., Zia-Ul-Haq, M., Abid Rashid, M., ... Moga, M. (2015). Scientific basis for use of *Pyrus pashia* Buch.-Ham. ex D. Don. fruit in gastrointestinal, respiratory and cardiovascular ailments. *PLoS One*, *10*(3), e0118605. doi:10.1371/journal.pone.0118605 PMID:25786248

Jang, E. M., Choi, M. S., Jung, U. J., Kim, M. J., Kim, H. J., Jeon, S. M., & Lee, M. K. (2008). Beneficial effects of curcumin on hyperlipidemia and insulin resistance in high-fat–fed hamsters. *Metabolism: Clinical and Experimental*, *57*(11), 1576–1583. doi:10.1016/j.metabol.2008.06.014 PMID:18940397

Jauhari, N., Bharadvaja, N., & Sharma, N. (2017). *Swertia chirata*: A comprehensive review with recent advances. *Current Pharmaceutical Biotechnology*, *18*(9), 730–739. doi:10.2174/1389201018666171026153515 PMID:29076426

Jayakumar, T., Hsieh, C. Y., Lee, J. J., & Sheu, J. R. (2013). Experimental and clinical pharmacology of *Andrographis paniculata* and its major bioactive phytoconstituent andrographolide. *Evidence-Based Complementary and Alternative Medicine*. PMID:23634174

Jayaprakash, R., Ramesh, V., Sridhar, M. P., & Sasikala, C. (2015). Antioxidant activity of ethanolic extract of *Tinospora cordifolia* on N-nitrosodiethylamine (diethyl nitrosamine) induced liver cancer in male Wister albino rats. *Journal of Pharmacy & Bioallied Sciences*, *7*(5S1), 40. doi:10.4103/0975-7406.155791 PMID:26015745

Jayaraman, R., Anitha, T., & Joshi, V. D. (2010). Analgesic and anticonvulsant effects of *Acorus calamus* roots in mice. *International Journal of Pharm Tech Research*, *2*(1), 552–555.

Jayasinghe, C., Gotoh, N., Aoki, T., & Wada, S. (2003). Phenolics composition and antioxidant activity of sweet basil (*Ocimum basilicum* L.). *Journal of Agricultural and Food Chemistry*, *51*(15), 4442–4449. doi:10.1021/jf034269o PMID:12848523

Jeyachandran, R., Xavier, T. F., & Anand, S. P. (2003). Antibacterial activity of stem extracts of *Tinospora cordifolia* (Willd) Hook. F and Thomson. *Ancient Science of Life*, *23*(1), 40–43. PMID:22557111

Jimoh, F. O., Adedapo, A. A., & Afolayan, A. J. (2010). Comparison of the nutritive value, antioxidant and antibacterial activities of *Sonchus asper* and *Sonchus oleraceus. Chem. Globe Pub*, *5*(1), 29–42.

Jing, Y., Nakajo, S., Xia, L., Nakaya, K., Fang, Q., Waxman, S., & Han, R. (1999). Boswellic acid acetate induces differentiation and apoptosis in leukemia cell lines. *Leukemia Research*, *23*(1), 43–50. doi:10.1016/S0145-2126(98)00096-4 PMID:9933134

Joharapurkar, A. A., Zambad, S. P., Wanjari, M. M., & Umathe, S. N. (2003). *In vivo* evaluation of antioxidant activity of ethanolic extract of *Rubia cordifolia* Linn.and its influence on ethanol-induced immunosuppression. *Indian Journal of Pharmacology*, *35*, 232–236.

Johnson, J. J., & Mukhtar, H. (2007). Curcumin for chemoprevention of colon cancer. *Cancer Letters*, *255*(2), 170–181. doi:10.1016/j.canlet.2007.03.005 PMID:17448598

Joseph, D. (2011). Pharmacotherapy, A pathophysiological approach, 8thedn, *The McGraw Hill companies*. *Inc.*, *2011*, 370.

Joshi, B. C., Mukhija, M., & Kalia, A. N. (2014). Pharmacognostical review of *Urtica dioica* L. *International Journal of Green Pharmacy*, *8*(4).

Joshi, H., & Parle, M. (2006). Antiamnesic effects of *Desmodium gangeticum* in mice. *Yakugaku Zasshi*, *126*(9), 795–804. doi:10.1248/yakushi.126.795 PMID:16946593

Joy, S., Sandipan, R., Dipankar, C., Aparna, L., & Krishnendu, A. (2012). Mycogenesis of gold nanoparticles using a phytopathogen *Alternaria alternata*. Bioproc. *Biosystems Engineering*, *35*, 637–643.

Judzentiene, A., Garjonyte, R., & Budiene, J. (2016). Variability, toxicity, and antioxidant activity of *Eupatorium cannabinum* (hemp agrimony) essential oils. *Pharmaceutical Biology*, *54*(6), 945–953. doi:10.3109/13880209.2015.1078384 PMID:26439817

Justesen, U., & Knuthsen, P. (2001). Composition of flavonoids in fresh herbs and calculation of flavonoid intake by use of herbs in traditional Danish dishes. *Food Chemistry*, *73*(2), 245–250. doi:10.1016/S0308-8146(01)00114-5

Kaleen, M., Asif, M., Ahmed, Q. U., & Bano, B. (2006). Antidiabetic and Antioxidant activity of *Annona squamosa* extract in streptorotocin induced diabetic rats. *Singapore Medical Journal*, *47*, 670–675. PMID:16865205

Kalikar, M. V., Thawani, V. R., Varadpande, U. K., Sontakke, S. D., Singh, R. P., & Khiyani, R. K. (2008). Immunomodulatory effect of *Tinospora cordifolia* extract in human immuno-deficiency virus positive patients. *Indian Journal of Pharmacology*, *40*(3), 107–110. doi:10.4103/0253-7613.42302 PMID:20040936

Kamala, A., Middha, S. K., Gopinath, C., Sindhura, H. S., & Karigar, C. S. (2018). *In vitro* antioxidant potentials of *Cyperus rotundus* L. rhizome extracts and their phytochemical analysis. *Pharmacognosy Magazine*, *14*(54), 261–267. doi:10.4103/pm.pm_228_17 PMID:29720842

Kamat, P. V., Flumiani, M., & Hartland, G. V. (1998). Picosecond dynamics of silver nanoclusters. Photoejection of electrons and fragmentation. *The Journal of Physical Chemistry B*, *102*(17), 3123–3128. doi:10.1021/jp980009b

Kamboj, A., & Saluja, A. K. (2008). *Ageratum conyzoides* L.: A review on its phytochemical and pharmacological profile. *Inter J of Green Pharma*, *2*(2), 59–68. doi:10.4103/0973-8258.41171

Kanedi, M., Rokiban, A., & Widodo, S., Nopiyansah, I., & Fauziah, L. (2016). Healing effect of leaf extract of candlebush (*Cassia alata* L.) on cutaneous wound infected with *Trichophyton rubrum. World Journal of Pharmaceutical and Life Sciences*, *2*(5), 42–50.

Kane, S. R., Apte, V. A., Todkar, S. S., & Mohite, S. K. (2009). Diuretic and laxative activity of ethanolic extract and its fractions of *Euphorbia thymifolia* Linn. *International Journal of Chemical Technology Research*, *1*, 149–152.

Kanitakis, J. (2002). Anatomy, histology and immunohistochemistry of normal human skin. *European Journal of Dermatology*, *12*(4), 390–401. PMID:12095893

Kannan, P., Ramadevi, S. R., & Hopper, W. (2009). Antibacterial activity of *Terminalia chebula* fruit extract. *African Journal of Microbiological Research*, *3*(4), 180–184.

Kapoor, L. D. (1990). *CRC Handbook of Ayurvedic medicinal plants*. Boca Raton, FL: CRC Press.

Kapur, P., Jarry, H., Wuttke, W., Pereira, B. M., & Seidlova-Wuttke, D. (2008). Evaluation of the antiosteoporotic potential of *Tinospora cordifolia* in female rats. *Maturitas*, *59*(4), 329–338. doi:10.1016/j.maturitas.2008.03.006 PMID:18482809

Kapur, P., Wuttke, W., Jarry, H., & Seidlova-Wuttke, D. (2010). Beneficial effects of β-Ecdysone on the joint, epiphyseal cartilage tissue and trabecular bone in ovariectomized rats. *Phytomedicine*, *17*(5), 350–355. doi:10.1016/j.phymed.2010.01.005 PMID:20171072

Kar, P. K., Murmu, S., Saha, S., Tandon, V., & Acharya, K. (2014). Anthelmintic efficacy of gold nanoparticles derived from a phytopathogenic fungus, *Nigrospora oryzae*. *PLoS One*, *9*(1), e84693. doi:10.1371/journal.pone.0084693 PMID:24465424

Kasote, D. M., Katyare, S. S., Hegde, M. V., & Bae, H. (2015). Significance of antioxidant potential of plants and its relevance to therapeutic applications. *International Journal of Biological Sciences*, *11*(8), 982–999. doi:10.7150/ijbs.12096 PMID:26157352

Kaufman, T., Kalderon, N., Ullmann, Y., & Berger, J. (1988). *Aloe vera* gel hindered wound healing of experimental second degree burns. *The Journal of Burn Care & Rehabilitation*, *9*(2), 156–159. doi:10.1097/00004630-198803000-00005 PMID:3360818

Kaur, A., Nain, P., & Nain, J. (2012). Herbal plants used in treatment of Rheumatoid arthritis: A review. *International Journal of Pharma Sciences*, *4*(4), 44–57.

Kaushik, R., Gupta, D., & Yadav, R. (2011). Alopecia: Herbal remedies. *International Journal of Pharmaceutical Sciences and Research*, *2*(7), 1631.

Kaushik, R., Mann Avninder, S., Sandhu, B. S., & Parihar, V. B. S. (2012). Green synthesis of gold nanoparticles using *Toona ciliata* methanol bark extract and their characterisation. *International research*. *Journal of Pharmaceutics*, *9*, 115–119.

Kawa, J. M., Taylor, C. G., & Przybylski, R. (2003). Buckwheat concentrate reduces serum glucose in streptozotocin-diabetic rats. *Journal of Agricultural and Food Chemistry*, *51*(25), 7287–7291. doi:10.1021/jf0302153 PMID:14640572

Keawpradub, N., Kirby, G. C., Steele, J. C. P., & Houghton, P. J. (1999). Antiplasmodial activity of extracts and alkaloids of three Alstonia species from Thailand. *Planta Medica*, *65*(08), 690–694. doi:10.1055-1999-14043 PMID:10630106

Kesarla, M. K., Badal, K. M., Madhulika, S., & Varadhan, K. (2012). *Terminalia chebula* mediated green and rapid synthesis of gold nanoparticles. *Spectrochimica Acta. Part A: Molecular and Biomolecular Spectroscopy*, *86*, 490–494. doi:10.1016/j.saa.2011.11.001 PMID:22130557

Kesik-Brodacka, M. (2017). Progress in biopharmaceutical development. *Biotechnology and Applied Biochemistry*, *65*(3), 306–322. doi:10.1002/bab.1617 PMID:28972297

Khan, A., Jabeen, K., & Iqbal, S. (2016). Antifungal activity of *Syzygium cumini* L. against Rhizoctoniasolani. *Pure and Applied Biology*, *5*(2), 193–199. doi:10.19045/bspab.2016.50025

Khandelwal, K. R. (2008). *Practical Pharmacognosy-Techniques and Experiments* (19th ed.). Pune: Nirali Prakashan.

Khan, S. W., & Khatoon, S. (2008). Ethnobotanical studies on some useful herbs of Haramosh and Bugrote valleys in Gilgit, northern areas of Pakistan. *Pakistan Journal of Botany*, *40*, 43–58.

Khare, C. P. (2007). *Indian medicinal plants: an illustrated dictionary*. New York: Springer-Verlag. doi:10.1007/978-0-387-70638-2

Khazaee-Pool, M., Pashaei, T., Jahangiry, L., Ponnet, K., & Gholami, A. (2017). Exploring breast cancer preventive lifestyle and social support of Iranian women: A study protocol for a mixed-methods approach. *International Journal for Equity in Health*, *16*(1), 97. doi:10.118612939-017-0592-0 PMID:28592298

Kim, B. W., Lee, E. R., Min, H. M., Jeong, H. S., Ahn, J. Y., Kim, J. H., ... Cho, S. G. (2008). Sustained ERK activation is involved in the kaempferol-induced apoptosis of breast cancer cells and is more evident under 3-D culture condition. *Cancer Biology & Therapy*, *7*(7), 1080–1089. doi:10.4161/cbt.7.7.6164 PMID:18443432

Kim, D. H., Hyun, S. K., Yoon, B. H., Seo, J.-H., Lee, K.-T., Cheong, J. H., & Ryu, J. H. (2009). Gluco-obtusifolin and its aglycon, obtusifolin, attenuate scopolamine-induced memory impairment. *Journal of Pharmacological Sciences*, *111*(2), 110–116. doi:10.1254/jphs.08286FP PMID:19834282

Kim, D. S. H. L., Park, S.-Y., & Kim, J.-Y. (2001). Curcuminoids from *Curcuma longa* L.(Zingiberaceae) that protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from βA (1–42) insult. *Neuroscience Letters*, *303*(1), 57–61. doi:10.1016/S0304-3940(01)01677-9 PMID:11297823

Kim, J., Park, S. H., Nam, S. W., & Choi, Y. H. (2012). Gastroprotective effect of selenium on ethanol-induced gastric damage in rats. *International Journal of Molecular Sciences*, *13*(5), 5740–5750. doi:10.3390/ijms13055740 PMID:22754328

Kim, K. J., Yu, H. H., Cha, J. D., Seo, S. J., Choi, N. Y., & You, Y. O. (2005). Antibacterial activity of *Curcuma longa* L. against methicillin-resistant *Staphylococcus aureus. Phytotherapy Research*, *19*(7), 599–604. doi:10.1002/ptr.1660 PMID:16161063

Kim, K., Kim, H., Kwon, J., Lee, S., Kong, H., Im, S. A., & Park, Y. I. (2009). Hypoglycemic and hypolipidemic effects of processed Aloe vera gel in a mouse model of non-insulin-dependent diabetes mellitus. *Phytomedicine*, *16*(9), 856–863. doi:10.1016/j.phymed.2009.02.014 PMID:19303272

Kim, Y. C., Kim, S. R., Markelonis, G. J., & Oh, T. H. (1998). Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. J Neurosci Res 53: 426-432. *Journal of Neuroscience Research*, *54*(1), 123–123. doi:10.1002/(SICI)1097-4547(19981001)54:1<123::AID-JNR13>3.0.CO;2-8 PMID:9778146

Kircheis, R., Halanek, N., Koller, I., Jost, W., Schuster, M., Gorr, G., ... Nechansky, A. (2012). Correlation of ADCC activity with cytokine release induced by the stably expressed, glyco-engineered humanized Lewis Y specific monoclonal antibody MB314. *mAbs*, *4*(4), 532–541. doi:10.4161/mabs.20577 PMID:22665069

Kirste, S., Treier, M., Wehrle, S. J., Becker, G., Abdel-Tawab, M., Gerbeth, K., & Momm, F. (2011). *Boswellia serrata* acts on cerebral edema in patients irradiated for brain tumors: A prospective, randomized, placebo-controlled, double-blind pilot trial. *Cancer*, *117*(16), 3788–3795. doi:10.1002/cncr.25945 PMID:21287538

Kirthikar, K. R., & Basu, B. D. (1999). *Indian medicinal plants* (2nd ed.). Popular Publication.

Kirtikar, K. R., & Basu, B. D. (1918). *Indian Medicinal Plants* (vol. 3). Academic Press.

Kirtikar, K. R., & Basu, B. D. (1933). Indian Medicinal Plants (vol. 2). Lalit Mohan Basu.

Kirtikar, K. R., & Basu, B. D. (1984). Indian medicinal plants. Delhi: Periodical Expert Agency.

Kleijnen, J., & Knipschild, P. (1992). *Ginkgo biloba* for cerebral insufficiency. *British Journal of Clinical Pharmacology*, *34*(4), 352–358. doi:10.1111/j.1365-2125.1992.tb05642.x PMID:1457269

Kloos, H. (1976). Preliminary studies of medicinal plants and plant products in Ethiopian markets. *Journal of Ethiopian Pharmaceutical Association*, *2*, 18–28.

Kobayashi, N., Suzuki, R., Koide, C., Suzuki, T., Matsuda, H., & Kubo, M. (1993). Effect of leaves of *Ginkgo biloba* on hair regrowth in C3H strain mice. *Yakugaku zasshi. Journal of the Pharmaceutical Society of Japan*, *113*(10), 718–724. doi:10.1248/yakushi1947.113.10_718 PMID:8254481

Kodancha, P., Kumar, S., Rajput, R., Patil, V., Udupa, A. L., Gupta, S., ... Shubha, H. V. (2011). Wound healing profile of *Asparagus racemosus* (Liliaceae) wild. *Current Pharma Research*, *1*(2), 111–114. doi:10.33786/JCPR.2011.v01i02.004

Koh, S. Y., Moon, J. Y., Unno, T., & Cho, S. K. (2019). Baicalein suppresses stem cell-like characteristics in radio and chemoresistant MDA-MB-231 human breast cancer cells through up-regulation of IFIT2. *Nutrients*, *11*(3), 624. doi:10.3390/nu11030624 PMID:30875792

Kokane, D. D., More, R. Y., Kale, M. B., Nehete, M. N., Mehendale, P. C., & Gadgoli, C. H. (2009). Evaluation of wound healing activity of root of *Mimosa pudica. Journal of Ethnopharmacology*, *124*(2), 311–315. doi:10.1016/j.jep.2009.04.038 PMID:19397984

Kokate, C. K., Purohit, A. P., & Gokhale, S. B. (2009). Text book of Pharmacognosy (44th ed.). New Delhi: Nirali Prakashan.

Kokate, C. K., Purohit, A. P., & Gokhale, S. B. (2007). *Pharmacognosy* (13th ed.). Pune: Nirali Prakashan Publisher.

Kokko, P. J. (1984). Site and mechanism of action of diuretics. *The American Journal of Medicine*, *77*(5), 11–17. doi:10.1016/S0002-9343(84)80003-0 PMID:6496555

Kolawole, O. T., & Ayankunle, A. A. (2012). Seasonal Variation in the Anti-Diabetic and Hypolipidemic Effects of Momordica charantia Fruit Extract in Rats. *European Journal of Medicinal Plants*, *2*(2), 177–185. doi:10.9734/EJMP/2012/998

Koo, S. I., & Noh, S. K. (2007). Green tea as inhibitor of the intestinal absorption of lipids: Potential mechanism for its lipid-lowering effect. *The Journal of Nutritional Biochemistry*, *18*(3), 179–183. doi:10.1016/j.jnutbio.2006.12.005 PMID:17296491

Kooti, W., Farokhipour, M., Asadzadeh, Z., Ashtary-Larky, D., & Asadi-Samani, M. (2016). The role of medicinal plants in the treatment of diabetes: A systematic review. *Electronic Physician*, *8*(1), 1832–1842. doi:10.19082/1832 PMID:26955456

Kopsell, D. A., & Kopsell, D. E. (2006). Accumulation and bioavailability of dietary carotenoids in vegetable crops. *Trends in Plant Science*, *11*(10), 499–507. doi:10.1016/j.tplants.2006.08.006 PMID:16949856

Kosaraju, J., Chinni, S., Roy, P. D., Kannan, E., Antony, A. S., & Kumar, M. S. (2014). Neuro-protective effect of *Tinospora cordifolia* ethanol extract on 6-hydroxy dopamine induced Parkinsonism. *Indian Journal of Pharmacology*, *46*(2), 176–180. doi:10.4103/0253-7613.129312 PMID:24741189

Kottaimuthu, R. (2008). Ethnobotany of the Valaiyans of Karandamalai, Dindigul District, Tamil Nadu, India. *Ethnobotanical Leaflets*, (1), 24.

Krishnaiah, D., Sarbatly, R., & Nithyanandam, R. (2011). A review of the antioxidant potential of medicinal plant species. *Food and Bioproducts Processing*, *89*(3), 217–233. doi:10.1016/j.fbp.2010.04.008

Krishnan, M., Jayaraj, R., Megala, J., & Namasivayam, E. (2014). Antioxidant mediated antiulcer effect of *Eupatorium triplinerve* Vahl against acetic acid induced ulcerative colitis in mice. *Biomedicine & Aging Pathology*, *4*(2), 153–160. doi:10.1016/j.biomag.2013.12.002

Krishnaraj, C., Seonhwa, S., & Soon-Il, Y. (2014). Effect of size and shape controlled biogenic synthesis of gold nanoparticles and their mode of interactions against food borne bacterial pathogens. *Arabian Journal of Chemistry*.

Krogstad, D. J., Gluzman, I. Y., Kyle, D. E., Oduola, A. M., Martin, S. K., Milhous, W. K., & Schlesinger, P. H. (1987). Efflux of chloroquine from *Plasmodium falciparum*: Mechanism of chloroquine resistance. *Science*, *238*(4831), 1283–1285. doi:10.1126cience.3317830 PMID:3317830

Kuang, P. G., Wu, W. P., Zhang, F. Y., Liu, J. X., & Pu, C. Q. (1989). The effect of radix Salviae miltiorrhizae on vasoactive intestinal peptide in cerebral ischemia: an animal experiment. *Journal of Traditional Chinese Medicine= Chung i tsa chih ying wen pan, 9*(3), 203-206.

Kuang, P., & Xiang, J. (1994). Effect of *Radix salviae* miltiorrhizae on EAA and IAA during cerebral ischemia in gerbils: a microdialysis study. *Journal of Traditional Chinese medicine= Chung i tsa chih ying wen pan, 14*(1), 45-50.

Kuang, P., Tao, Y., & Tian, Y. (1996). Effect of radix Salviae miltiorrhizae on nitric oxide in cerebral ischemic-reperfusion injury. *Journal of Traditional Chinese Medicine= Chung i tsa chih ying wen pan, 16*(3), 224-227.

Kuang, P., Wu, W., Liu, J., Zhang, F., & Pu, C. (1991). The effect of radix Salviae Miltiorrhizae (RSM) on substance P in cerebral ischemia--animal experiment. *Journal of traditional Chinese medicine= Chung i tsa chih ying wen pan, 11*(2), 123-127.

Kulkarni, C., Pattanshetty, J. R., & Amruthraj, G. (1988). Effect of alcoholic extract of *Clitoria ternatea* Linn. on central nervous system in rodents. *Indian Journal of Experimental Biology*, *26*(12), 957–960. PMID:3254867

Kumar, D. (2013). *Pharmaceutical and pharmacological activities of Hibiscus rosa sinensis mucilage* (vol. 2). Academic Press.

Kumar, A., Gnananath, K., Gande, S., Goud, E., Rajesh, P., & Nagarjuna, S. (2011). Anti-diabetic Activity of Ethanolic Extract of Achyranthes aspera Leaves in Streptozotocin induced diabetic rats. *Journal of Pharmacy Research*, *4*(7), 3124–3125.

Kumar, A., Ilavarasan, R., Jayachandran, T., Deecaraman, M., Kumar, R. M., & Aravindan, P. (2008). Anti-inflammatory activity of *Syzygium cumini* seed. *African Journal of Biotechnology*, *7*(8), 941–943.

Kumar, A., Padmanabhan, N., & Krishana, M. R. V. (2007). Central nervous system activity of *Syzigium cumini* seeds. *Pakistan Journal of Nutrition*, *6*(6), 698–700. doi:10.3923/pjn.2007.698.700

Kumar, A., Rahal, A., & Verma, A. K. (2011). *In-vitro* antibacterial activity of hot aqueous extract (HAE) of *Ocimum sanctum* (Tulsi) leaves. *Indian Journal of Veterinary Medicine*, *31*, 96–97.

Kumarasamy, K. K., Toleman, M. A., Walsh, T. R., Bagaria, J., Butt, F., Balakrishnan, R., ... Woodford, N. (2010). Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. *The Lancet. Infectious Diseases*, *10*(9), 597–602. doi:10.1016/S1473-3099(10)70143-2 PMID:20705517

Kumar, D. B., Mitra, A., & Manjunatha, M. (2011). Azadirachtolide. *Pharmacognosy Communications*, *1*(1), 78–84. doi:10.5530/pc.2011.1.5

Kumar, D., Kumar, V., & Jalwal, P. (2016). Boswellic Acid-Potential tumors suppressant terpenoid-Photochemistry, Extraction and Isolation Methods-A comprehensive review study. *Journal of Pharmacognosy and Phytochemistry*, *5*(3), 231.

Kumar, D., Parcha, V., Maithani, A., & Dhulia, I. (2012). Effect and evaluation of antihyperlipidemic activity guided isolated fraction from total methanol extract of *Bauhinia variegata* (Linn.) in triton WR-1339 induced hyperlipidemic rats. *Asian Pacific Journal of Tropical Disease*, *2*(2), 909–913. doi:10.1016/S2222-1808(12)60290-4

Kumar, E. K., Mastan, S. K., Reddy, K. R., Reddy, G. A., Raghunandan, N., & Chaitanya, G. (2008). Antiarthritic property of methanolic extract of *Syzygium cumini* seeds. *International Journal of Integrative Biology*, *4*, 55.

Kumar, G. S., Nayaka, H., Dharmesh, S. M., & Salimath, P. V. (2006). Free and bound phenolic antioxidants in amla (*Emblica officinalis*) and turmeric (*Curcuma longa*). *Journal of Food Composition and Analysis*, *19*(5), 446–452. doi:10.1016/j.jfca.2005.12.015

Kumari, A., & Kakkar, P. (2008). Screening of antioxidant potential of selected barks of indian medicinal plants by multiple in vitro assays. *Biomedical and Environmental Sciences*, *21*(1), 24–29. doi:10.1016/S0895-3988(08)60003-3 PMID:18478975

Kumar, J., Mitra, M. D., Hussain, A., & Kaul, G. (2019). Exploration of immunomodulatory and protective effect of *Withania somnifera* on trace metal oxide (zinc oxide nanoparticles) induced toxicity in Balb/c mice. *Molecular Biology Reports*, *46*(2), 2447–2459. doi:10.100711033-019-04705-x PMID:30847852

Kumar, K., Mruthunjaya, K., Kumar, S., & Mythreyi, R. (2013). Antiulcer activity of ethanol extract of the stem bark of *Careya arborea* Roxb. *International Current Pharmaceutical Journal*, *2*(3), 78–82. doi:10.3329/icpj.v2i3.13633

Kumar, M. S., Sripriya, R., Raghavan, H. V., & Sehgal, P. K. (2006). Wound healing potential of *Cassia fistula* on infected albino rat model. *The Journal of Surgical Research*, *131*(2), 283–289. doi:10.1016/j.jss.2005.08.025 PMID:16242721

Kumar, M., Bussmann, R. W., Joshi, M., & Kumar, P. (2011). Ethnomedicinal uses of plants close to rural habitation in Garhwal Himalaya, India. *Journal of Medicinal Plants Research*, *5*(11), 2252–2260.

Kumar, R. P., Shammy, J., Nitin, G., & Rinu, R. (2014). An inside review of *Amaranthus spinosus* Linn: A potential medicinal plant of India. *International Journal of Research in Pharmacy and Chemistry*, *4*(3), 643–653.

Kumar, R., Roopan, S. M., Prabhakarn, A., Khanna, V. G., & Chakroborty, S. (2012). Agricultural waste Annona squamosa peel extract: Biosynthesis of silver nanoparticles. *Spectra Acta. A Mol. Biomol. Spectrosc.*, *90*, 173–176. doi:10.1016/j.saa.2012.01.029 PMID:22336049

Kumar, R., Sharma, B., Tomar, N. R., Roy, P., Gupta, A. K., & Kumar, A. (2011). In vivo evolution of hypoglycemic activity of *Aloe* spp. And identification of its mode of action on GLUT-4 gene expression in vitro. *Applied Biochemistry and Biotechnology*, *164*(8), 1246–1256. doi:10.100712010-011-9210-6 PMID:21409411

Kumar, S., Yadav, A., Yadav, M., & Yadav, J. P. (2017). Effect of climate change on phytochemical diversity, total phenolic content and *in vitro* antioxidant activity of *Aloe vera* (L.) Burm.f. *BMC Research Notes*, *10*(1), 60. doi:10.118613104-017-2385-3 PMID:28118858

Kumar, V., & Van Staden, J. (2016). A review of *Swertia chirayita* (Gentianaceae) as a traditional medicinal plant. *Frontiers in Pharmacology*, *6*, 308. doi:10.3389/fphar.2015.00308 PMID:26793105

Kumar, Y. R., & Rajani, G. P. (2011). Analgesic and anti-ulcer activities of ethanol and aqueous extracts of root of *Bauhinia variegate* Linn. *International Journal of Pharmacology*, *7*(5), 616–622. doi:10.3923/ijp.2011.616.622

Kuo, Y. H., & Li, Y. C. (1997). Constituents of the bark of *Ficus microcarpa* L.f. *Journal of the Chinese Chemical Society (Taipei)*, *44*(3), 321–325. doi:10.1002/jccs.199700048

Kuppast, I. J., & Nayak, P. V. (2005). Wound healing activity of *Cordia dichotoma* Forst. f. fruits. *Research article, 5*(2), 99-102.

Kwon, O. S., Han, J. H., Yoo, H. G., Chung, J. H., Cho, K. H., Eun, H. C., & Kim, K. H. (2007). Human hair growth enhancement *in vitro* by green tea epigallocatechin-3-gallate (EGCG). *Phytomedicine*, *14*(7-8), 551–555. doi:10.1016/j.phymed.2006.09.009 PMID:17092697

Labban, L. (2014). Medicinal and pharmacological properties of Turmeric (*Curcuma longa*): A review. *International Journal of Pharma and Bio Sciences*, *5*(1), 17–23.

Laishram, A., Naik, J., Reddy, S., & Jayasimha Rayalu, D. (2013). Phytochemical analysis, TLC profiling and antimicrobial activity of *Tephrosia purpurea. International Journal of Pharmacy & Life Sciences*, *4*(2), 2375–2379.

Lai, X. Y., Liang, H., & Zhao, Y. Y. (2002). A survey of the studies on chemical constituents and pharmacological activities of Acorus plants. *Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi=. Zhongguo Zhongyao Zazhi*, *27*(3), 161–165. PMID:12807142

Lang, S. J., Schmiech, M., Hafner, S., Paetz, C., Steinborn, C., Huber, R., ... Simmet, T. (2019). Antitumor activity of an *Artemisia annua* herbal preparation and identification of active ingredients. *Phytomedicine*, *62*, 152962. doi:10.1016/j.phymed.2019.152962 PMID:31132755

Lavie, D., Willner, D., & Merenlender, Z. (1964). Constituents of *Citrullus colocynthis* (L.) Schrad. *Phytochemistry*, *3*(1), 51–56. doi:10.1016/S0031-9422(00)83994-1

Lawrence, S. (2005). Biotech drug market steadily expands. *Nature Biotechnology*, *23*(12), 14–66. doi:10.1038/nbt1205-1466 PMID:16333279

Lawrence, S. (2007). Pipelines turn to biotech. *Nature Biotechnology*, *25*(12), 13–42. doi:10.1038/nbt1207-1342 PMID:18066015

Lee, H.-B., & Han, W. (2014). Unique Features of Young Age Breast Cancer and Its Management. *Journal of Breast Cancer*, *17*(4), 301–307. doi:10.4048/jbc.2014.17.4.301 PMID:25548576

Lee, J., Son, D., Lee, P., Kim, D. K., Shin, M. C., Jang, M. H., ... Kim, H. (2003). Protective effect of methanol extract of *Uncaria rhynchophylla* against excitotoxicity induced by N-methyl-D-aspartate in rat hippocampus. *Journal of Pharmacological Sciences*, *92*(1), 70–73. doi:10.1254/jphs.92.70 PMID:12832857

Lemonnier, N., Zhou, G. B., Prasher, B., Mukerji, M., Chen, Z., Brahmachari, S. K., & Sagner, M. (2017). Traditional knowledge-based medicine: a review of history, principles, and relevance in the present context of P4 systems medicine. *Progress in Preventive Medicine, 2*(7), e0011.

Lev, E. (2006). Ethno-diversity within current ethno-pharmacology as part of Israeli traditional medicine–A review. *Journal of Ethnobiology and Ethnomedicine*, *2*(1), 4. doi:10.1186/1746-4269-2-4 PMID:16401348

Lexa, A., Fleurentins, J., Lehr, P. R., Mortier, F., Pruvost, M., & Pelt, J. M. (1989). Choleretic and hepatoprotective properties of *Eupatorium cannabinum* in the rat. *Planta Medica*, *55*(02), 127–132. doi:10.1055-2006-961904 PMID:2748727

Li, A., Gao, M., Zhao, N., Li, P., Zhu, J., & Li, W. (2019). Acute liver failure associated with Fructus Psoraleae: A case report and literature review. *BMC Complementary and Alternative Medicine*, *19*(1), 1–4. doi:10.118612906-019-2493-9 PMID:30975110

Liao, B., Newmark, H., & Zhou, R. (2002). Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. *Experimental Neurology*, *173*(2), 224–234. doi:10.1006/exnr.2001.7841 PMID:11822886

Li, C., Yang, J., Yu, S., Chen, N., Xue, W., Hu, J., & Zhang, D. (2008). Triterpenoid saponins with neuroprotective effects from the roots of *Polygala tenuifolia. Planta Medica*, *74*(02), 133–141. doi:10.1055-2008-1034296 PMID:18256974

Li, D. D., Chen, J. H., Chen, Q., Chen, Q., Li, G. W., Yue, J. M., ... Shen, X. (2005). *Swietenia mahagony* extract shows agonistic activity to PPAR and gives ameliorative effects on diabetic db/db mice. *Acta Pharmacol*, *26*(2), 220–222. doi:10.1111/j.1745-7254.2005.00527.x PMID:15663902

Li, J., Wang, Q., Wang, Z., Cui, N., Yang, B., Niu, W., & Kuang, H. (2019). Tetrandrine inhibits colon carcinoma HT-29 cells growth via the Bcl-2/Caspase 3/PARP pathway and G1/S phase. *Bioscience Reports*, *39*(5), BSR20182109. doi:10.1042/BSR20182109 PMID:31040202

Lima, C. F., Valentao, P. C. R., Andrade, P. B., Seabra, R. M., Fernandes-Ferreira, M., & Pereira-Wilson, C. (2007). Water and methanolic extracts of Salvia officinalis protect HepG2 cells from t-BHP induced oxidative damage. *Chemico-Biological Interactions*, *167*(2), 107–115. doi:10.1016/j.cbi.2007.01.020 PMID:17349617

Lim, S. J. (2007). Effects of fractions of *Benincasa hispida* on antioxidative status in streptozotocin induced diabetic rats. *Journal of Nutrition and Health*, *40*(4), 295–302. doi:10.4163/jnh.2018.51.4.295

Lingesh, A., Paul, D., Naidu, V. G. M., & Satheeshkumar, N. (2019). AMPK activating and anti adipogenic potential of *Hibiscus rosa sinensis* flower in 3T3-L1 cells. *Journal of Ethnopharmacology*, *233*, 123–130. doi:10.1016/j.jep.2018.12.039 PMID:30593890

Lin, Y. S., Chiu, Y. C., Tsai, Y. H., Tsai, Y. F., Wang, J. Y., Tseng, L. M., & Chiu, J. H. (2019). Different mechanisms involved in the berberine-induced antiproliferation effects in triple-negative breast cancer cell lines. *Journal of Cellular Biochemistry*, *120*(8), 13531–13544. doi:10.1002/jcb.28628 PMID:30957305

Lipinski, B. (2001). Pathophysiology of oxidative stress in diabetes mellitus. *Journal of Diabetes and Its Complications*, *15*(4), 203–210. doi:10.1016/S1056-8727(01)00143-X PMID:11457673

Lipschitz, W. L., Hadidian, Z., & Kerpcsar, A. (1943). Bioassay of diuretics. *The Journal of Pharmacology and Experimental Therapeutics*, *79*, 97–110.

Liu, C., Hu, M. Y., Zhang, M., Li, F., Li, J., Zhang, J., & Liu, X. D. (2014). Association of GLP-1 secretion with anti-hyperlipidemic effect of ginsenosides in high-fat diet fed rats. *Metabolism: Clinical and Experimental*, *63*(10), 1342–1351. doi:10.1016/j.metabol.2014.06.015 PMID:25060691

Liu, J. J., & Duan, R. D. (2009). LY294002 enhances boswellic acid-induced apoptosis in colon cancer cells. *Anticancer Research*, *29*(8), 2987–2991. PMID:19661305

Liu, J. J., Nilsson, A., Oredsson, S., Badmaev, V., Zhao, W. Z., & Duan, R. D. (2002). Boswellic acids trigger apoptosis via a pathway dependent on caspase-8 activation but independent on Fas/Fas ligand interaction in colon cancer HT-29 cells. *Carcinogenesis*, *23*(12), 2087–2093. doi:10.1093/carcin/23.12.2087 PMID:12507932

Liu, L., & Yeh, Y. Y. (2001). Water-soluble organosulfur compounds of garlic inhibit fatty acid and triglyceride syntheses in cultured rat hepatocytes. *Lipids*, *36*(4), 395–400. doi:10.100711745-001-0734-4 PMID:11383692

Liu, P., Hu, Y., Guo, D.-H., Lu, B.-R., Rahman, K., Mu, L.-H., & Wang, D.-X. (2010). Antioxidant activity of oligosaccharide ester extracted from *Polygala tenuifolia* roots in senescence-accelerated mice. *Pharmaceutical Biology*, *48*(7), 828–833. doi:10.3109/13880200903283707 PMID:20645784

Liu, T., Liu, X., & Li, W. (2016). Tetrandrine, a Chinese plant-derived alkaloid, is a potential candidate for cancer chemotherapy. *Oncotarget*, *7*(26), 40800. doi:10.18632/oncotarget.8315 PMID:27027348

Liu, W. K., Xu, S. X., & Che, C.-T. (2000). Anti-proliferative effect of ginseng saponins on human prostate cancer cell line. *Life Sciences*, *67*(11), 1297–1306. doi:10.1016/S0024-3205(00)00720-7 PMID:10972198

Li, X. Z., & Nikaido, H. (2004). Efflux-mediated drug resistance in bacteria. *Drugs*, *64*(2), 159–204. doi:10.2165/00003495-200464020-00004 PMID:14717618

Li, X., Sun, B., Zhu, C. J., Yuan, H. Q., Shi, Y. Q., Gao, J., ... Lou, H. X. (2009). Reversal of p-glycoprotein-mediated multidrug resistance by macrocyclic bisbibenzyl derivatives in adriamycin-resistant human myelogenous leukemia (K562/A02) cells. *Toxicology In Vitro*, *23*(1), 29–36. doi:10.1016/j.tiv.2008.09.015 PMID:18938236

Llaca-Díaz, J. M., Mendoza-Olazarán, S., Camacho-Ortiz, A., Flores, S., & Garza-González, E. (2012). One-year surveillance of ESKAPE pathogens in an intensive care unit of monterrey, Mexico. *Chemotherapy*, *58*(6), 475–481. doi:10.1159/000346352 PMID:23548324

Lombardero, M., Kovacs, K., & Scheithauer, B. W. (2011). Erythropoietin: A hormone with multiple functions. *Pathobiology*, *78*(1), 41–53. doi:10.1159/000322975 PMID:21474975

Lone, A. H., Ahmad, T., Anwar, M., Sofi, G., Imam, H., & Habib, S. (2012). Perception of health promotion in Unani herbal medicine. *Journal of Herbal Medicine*, *2*(1), 1–5. doi:10.1016/j.hermed.2012.02.003

López, V., Martín, S., Gómez-Serranillos, M. P., Carretero, M. E., Jäger, A. K., & Calvo, M. I. (2009). Neuroprotective and neurological properties of *Melissa officinalis. Neurochemical Research*, *34*(11), 1955–1961. doi:10.100711064-009-9981-0 PMID:19760174

Lou, H. X., Li, G. Y., & Wang, F. Q. (2002). A cytotoxic diterpenoid and antifungal phenolic compounds from *Frullania muscicola* Steph. *Journal of Asian Natural Products Research*, *4*(2), 87–94. doi:10.1080/10286020290027353 PMID:12067164

Lourith, N., & Kanlayavattanakul, M. (2013). Hair loss and herbs for treatment. *Journal of Cosmetic Dermatology*, *12*(3), 210–222. doi:10.1111/jocd.12051 PMID:23992163

Luanpitpong, S., Nimmannit, U., Pongrakhananon, V., & Chanvorachote, P. (2011). *Emblica* (*Phyllanthus emblica* Linn.) fruit extract promotes proliferation in dermal papilla cells of human hair follicle. *Research Journal of Medicinal Plant*, *5*(1), 95–100. doi:10.3923/rjmp.2011.95.100

Lu, J.-M., Yao, Q., & Chen, C. (2009). Ginseng compounds: An update on their molecular mechanisms and medical applications. *Current Vascular Pharmacology*, *7*(3), 293–302. doi:10.2174/157016109788340767 PMID:19601854

Lu, M. (2013). Status and trends of chinese traditional medicine industry. Chin. *Indian Journal of Pharmaceutical Sciences*, *44*, 214–216.

Luo, L., Wang, J. N., Kong, L. D., Jiang, Q. G., & Tan, R. X. (2000). Antidepressant effects of Banxia Houpu decoction, a traditional Chinese medicinal empirical formula. *Journal of Ethnopharmacology*, *73*(1-2), 277–281. doi:10.1016/S0378-8741(00)00242-7 PMID:11025166

Lu, Z. Q., Fan, P. H., Ji, M., & Lou, H. X. (2006). Terpenoids and bisbibenzyls from Chinese liverworts *Conocephalum conicum* and *Dumortiera hirsuta. Journal of Asian Natural Products Research*, *8*(1-2), 187–192. doi:10.1080/1028602042000325537 PMID:16753803

Ly, M., Antoine, M., André, F., Callard, P., Bernaudin, J. F., & Diallo, D. A. (2011). Breast cancer in Sub-Saharan African women [review]. *Bulletin du Cancer*, *98*(7), 797–806. doi:10.1684/bdc.2011.1392 PMID:21700549

Magner, L. N. (1992). *A history of medicine*. New York: Marcel Dekker Inc.

Mahadeva, U. S., Ahmad, B. O., Mohd, K. S., & Zin, T. (2016). The Antiulcer activity of *Musa paradisiaca* (banana) tepal and skin extracts in ulcer induced albino mice. *The Malaysian Journal of Analytical Sciences*, *20*(5), 1203–1216. doi:10.17576/mjas-2016-2005-27

Mahapatra, P. K., Chakraborty, D., & Chaudhuri, A. N. (1986). Anti-inflammatory and antipyretic activities of *Syzygium cuminii. Planta Medica*, *52*(6), 540. doi:10.1055-2007-969339 PMID:17345495

Mahmood, A. A., Mariod, A. A., Bayaty, F. A., & Wahab, S. I. A. (2010). An anti-ulcerogenic activity of *Gynura procumbens* leaf extract extracts against experimentally-induced gastric lesions in rats. *Journal of Medicinal Plants Research*, *4*(8), 685–691.

Maiga, A., Malterud, K. E., Diallo, D., & Paulsen, B. S. (2006). Antioxidant and 15-lipoxygenase inhibitory activities of the Malian medicinal plants *Diospyros abyssinica* (Hiern) F. White (Ebenaceae), *Lannea velutina* A. Rich (Anacardiaceae) and *Crossopteryx febrifuga* (Afzel) Benth. (Rubiaceae). *Journal of Ethnopharmacology*, *104*(1-2), 132–137. doi:10.1016/j.jep.2005.08.063 PMID:16213686

Maiti, A., Dewanjee, S., & Mandal, S. C. (2007). *In vivo* evaluation of antidiarrhoeal activity of the seed of *Swietenia macrophylla* King (Meliaceae). *Tropical Journal of Pharmaceutical Research*, *6*(2), 711–716. doi:10.4314/tjpr.v6i2.14650

Ma, J. K., Drake, P. M., & Christou, P. (2003). Genetic modification: The production of recombinant pharmaceutical proteins in plants. *Nature Reviews. Genetics*, *4*(10), 794–805. doi:10.1038/nrg1177 PMID:14526375

Majid, M. A., Rahman, I. M. M., Shipar, M. A. H., Uddin, M. H., & Chowdhury, Y. R. (2004). Physico-chemical characterization, antimicrobial activity and toxicity analysis of *Swietenia mahagoni* seed oil. *International Journal of Agriculture and Biology*, *6*, 350–354.

Malik, J. K., Manvi, F. V., Nanjware, B. R., & Sanjiv, S. (2009). Wound healing properties of alcoholic extract of *Gymnema sylvestre* R. Br. leaves in rats. *Journal of Pharmacy Research*, *2*(6), 1029–1030.

Malik, T. A., Kamili, A. N., Chishti, M. Z., Ahad, S., Tantry, M. A., Hussain, P. R., & Johri, R. K. (2017). Breaking the resistance of *Escherichia coli*: Antimicrobial activity of *Berberis lycium* Royle. *Microbial Pathogenesis*, *102*, 12–20. doi:10.1016/j.micpath.2016.11.011 PMID:27888048

Mallikarjuna, R., Prasad, S. H. K. R., & Jyothirmayi, N. (2012). Efficacy of ripened and unripened fruit extracts of *Musa X Paradisiaca L. (Bontha Cultivar)* against human pathogens. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(1), 457–458.

Mallikarjun, S., Rao, A., Rajesh, G., Shenoy, R., & Pai, M. (2016). Antimicrobial efficacy of Tulsi leaf (*Ocimum sanctum*) extract on periodontal pathogens: An in vitro study. *Journal of Indian Society of Periodontology*, *20*(2), 145–150. PMID:27143825

Mallik, P., Mishra, S. K., & Satapathy, K. B. (2014). Studies on the antibacterial and antioxidant activities of *Sonchus asper* (L.) Hill and *Seseli diffusum* (Roxb. Ex sm.) Sant. & Wagh. *ISOR J. Pharma. Bio. Sci*, *9*(6), 24–27. doi:10.9790/3008-09642427

Maltas, E., & Yildiz, S. (2012). Evaluation of phytochemicals and antioxidant activity of *Ginkgo biloba* from Turkey. *Pharmacology*, *3*, 113–120.

Mandal, S. K., Mandal, S. C., Pal, M., & Syr, T. (2004). Antiulcer activity of ethanol extract of *Eupatorium adenophorum* leaf. *Indian J. Nat. Prod.*, *20*(2), 23–25.

Manjula, S., & Mamidala, E. (2013). An ethnobotanical survey of medicinal plants used by traditional healers of Thadvai, Warangal district, Andhra Pradesh, India. *International Journal of Medical Research and Health Sciences*, *2*(1), 40–46.

Manjunatha, B. K., Krishna, V., Vidya, S. M., Mankani, K. L., & Manohara, Y. N. (2007). Wound healing activity of *Lycopodium serratum. Indian Journal of Pharmaceutical Sciences*, *69*(2), 283–287. doi:10.4103/0250-474X.33159

Mannino, G., Occhipinti, A., & Maffei, M. (2016). Quantitative determination of 3-O-acetyl-11-keto-β-boswellic acid (AKBA) and other boswellic acids in *Boswellia sacra* Flueck (syn. B. *carteri Birdw*) and *Boswellia serrata* Roxb. *Molecules (Basel, Switzerland)*, *21*(10), 1329. doi:10.3390/molecules21101329 PMID:27782055

Mansi, K., Abushoffa, A. M., Disi, A., & Aburjai, T. (2009). Hypolipidemic effects of seed extract of celery (*Apium graveolens*) in rats. *Pharmacognosy Magazine*, *5*(20), 301. doi:10.4103/0973-1296.58149

Manukumar, H. M., Shiva Kumar, J., Chandrasekhar, B., Raghava, S., & Umesha, S. (2017). Evidences for diabetes and insulin mimetic activity of medicinal plants: Present status and future prospects. *Critical Reviews in Food Science and Nutrition*, *57*(12), 2712–2729. doi:10.1080/10408398.2016.1143446 PMID:26857927

Mariath, I. R., Falcão, H. S., Barbosa-Filho, J. M., Sousa, L. C. F., Tomaz, A. C. A., Batista, L. M., ... Cunha, E. V. L. (2009). Plants of the American continent with antimalarial activity. *Revista Brasileira de Farmacognosia*, *19*(1a), 158–191. doi:10.1590/S0102-695X2009000100026

Marti, A., Bock, J. E., Pagani, M. A., Ismail, B., & Seetharaman, K. (2016). Structural characterization of proteins in wheat flour doughs enriched with intermediate wheatgrass (*Thinopyrum intermedium*) flour. *Food Chemistry*, *194*, 994–1002. doi:10.1016/j.foodchem.2015.08.082 PMID:26471645

Martin, S. K., Oduola, A. M., & Milhous, W. K. (1987). Reversal of chloroquine resistance in *Plasmodium falciparum* by verapamil. *Science*, *235*(4791), 899–901. doi:10.1126cience.3544220 PMID:3544220

Marwat, S. K., Rehman, F., & Khan, A. A. (2016). Phytochemistry and pharmacological values of rocket (*Eruca sativa* Miller) - A review. *International Journal of Horticulture*, *6*(21), 1–7. doi:10.5376/ijh.2016.06.0016

Matsuda, H., Yamazaki, M., Asanuma, Y., & Kubo, M. (2003). Promotion of hair growth by ginseng radix on cultured mouse vibrissal hair follicles. *Phytotherapy Research*, *17*(7), 797–800. doi:10.1002/ptr.1241 PMID:12916080

Mattill, H. A. (1947). Antioxidants. *Annual Review of Biochemistry*, *16*(1), 177–192. doi:10.1146/annurev.bi.16.070147.001141 PMID:20259061

Mazid, M., Khan, T. A., & Mohammad, F. (2012). Medicinal plants of rural India: A review of use by Indian folks. *Indo Global Journal of Pharmaceutical Sciences*, *2*(3), 286–304.

Mazza, G. (1985). Gas chromatographic and mass spectrometric studies of the constituents of the rhizome of calamus: I. The volatile constituents of the essential oil. *Journal of Chromatography. A*, *328*, 179–194. doi:10.1016/S0021-9673(01)87389-1

McGrath, S. P., & Zhao, F. J. (2003). Phytoextraction of metals and metalloids from contaminated soils. *Current Opinion in Biotechnology*, *14*(3), 277–282. doi:10.1016/S0958-1669(03)00060-0 PMID:12849780

Meeran, S. M., Katiyar, S., & Katiyar, S. K. (2008). Berberine-induced apoptosis in human prostate cancer cells is initiated by reactive oxygen species generation. *Toxicology and Applied Pharmacology*, *229*(1), 33–43. doi:10.1016/j.taap.2007.12.027 PMID:18275980

Mehdiyeva, N. P., Serkerov, S. V., & Bahshaliyeva, K. F. (2010). Chemical composition and antifungal activities of the essential oils of from the flora Azerbaijan. *Chemistry of Plant Raw Material*, *2*, 139–142.

Mehrotra, R., Katiyar, C. K., & Gupta, A. P. (2000). *Hepatoprotective composition and composition for treatment of conditions related to hepatitis band E infection*. US Patent, 6, 136, 316.

Menon, M. K., & Kar, A. (1971). Analgesic and psychopharmacological effects of the gum resin of *Boswellia serrata*. *Planta Medica*, *19*(2), 333–341. doi:10.1055-0028-1099651 PMID:5573545

Merhan, O. (2017). The biochemistry and antioxidant properties of carotenoids. In *Carotenoids*. InTech. doi:10.5772/67592

Merken, H. M., & Beecher, G. R. (2000). Measurement of food flavonoids by high-performance liquid chromatography: A review. *Journal of Agricultural and Food Chemistry*, *48*(3), 577–599. doi:10.1021/jf990872o PMID:10725120

Meyer, A. J., & Hell, R. (2005). Glutathione homeostasis and redox-regulation by sulfhydryl groups. *Photosynthesis Research*, *86*(3), 435–457. doi:10.100711120-005-8425-1 PMID:16315075

Miah, M. A. H., Hasan, M., Sarker, Y. A., Alam, M. M., & Juyena, N. S. (2017). Clinical evaluation of ethanolic extract of curcumin (*Curcuma longa*) on wound healing in Black Bengal goats. *Journal of Advanced Veterinary and Animal Research*, *4*(2), 181–186. doi:10.5455/javar.2017.d209

Miguel, M. G. (2010). Antioxidant activity of medicinal and aromatic plants. A review. *Flavour and Fragrance Journal*.

Mirza, M., Navaei, M. N., & Dini, M. (2006). Volatile constituents of essential oils isolated from flowers and leaves of *Eupatorium cannabinum* L. from Iran. *Iranian Journal of Pharmaceutical Research*, *2*, 149–152.

Mishra, K., Dash, A. P., & Dey, N. (2011). Andrographolide: A novel antimalarial diterpene lactone compound from *Andrographis paniculata* and its interaction with curcumin and artesunate. *Journal of Tropical Medicine*, *2011*(365645), 1–6. doi:10.1155/2011/579518 PMID:21760808

Mishra, P. R., Panda, P. K., Apanna, K. C., & Panigrahi, S. (2011). Evaluation of acute hypolipidemic activity of different plant extracts in Triton WR-1339 induced hyperlipidemia in albino rats. *Pharmacologyonline*, *3*, 925–934.

Mishra, R., & Kaur, G. (2013). Aqueous ethanolic extract of *Tinospora cordifolia* as a potential candidate for differentiation-based therapy of glioblastomas. *PLoS One*, *8*(10), e78764. doi:10.1371/journal.pone.0078764 PMID:24205314

Mishra, R., & Kaur, G. (2015). *Tinospora cordifolia* induces differentiation and senescence pathways in neuroblastoma cells. *Molecular Neurobiology*, *52*(1), 719–733. doi:10.100712035-014-8892-5 PMID:25280667

Mishra, R., Pandey, V. K., & Chandra, R. (2014). Potential of Bryophytes as therapeutics. *International Journal of Pharmaceutical Sciences and Research*, *5*(9), 3584–3593.

Mishra, S. B., Mukerjee, A., & Vijayakumar, M. (2010). Wound healing activity of the aqueous alcoholic extract of *Jasminum grandiflorum* Linn leaves. *Pharmacologyonline*, *3*, 35–40.

Mittler, R. (2017). ROS Are Good. *Trends in Plant Science*, *22*(1), 11–19. doi:10.1016/j.tplants.2016.08.002 PMID:27666517

Miyasaki, Y., Rabenstein, J. D., Rhea, J., Crouch, M. L., Mocek, U. M., Kittell, P. E., ... Liu, G. Y. (2013). Isolation and characterization of antimicrobial compounds in plant extracts against multidrug-resistant *Acinetobacter baumannii. PLoS One*, *8*(4), e61594. doi:10.1371/journal.pone.0061594 PMID:23630600

Mizumaki, Y., Kurimoto, M., Hirashima, Y., Nishijima, M., Kamiyama, H., Nagai, S., & Endo, S. (2002). Lipophilic fraction of *Panax ginseng* induces neuronal differentiation of PC12 cells and promotes neuronal survival of rat cortical neurons by protein kinase C dependent manner. *Brain Research*, *950*(1-2), 254–260. doi:10.1016/S0006-8993(02)03049-4 PMID:12231251

Mizuno, Y. (2014). Recent research progress in and future perspective on treatment of Parkinson's disease. *Integrative Medicine International*, *1*(2), 67–79. doi:10.1159/000365571

Mobasseri, M., Payahoo, L., Ostadrahimi, A., Bishak, Y. K., Jafarabadi, M. A., & Mahluji, S. (2014). *Anethum graveolens* supplementation improves insulin sensitivity and lipid abnormality in type 2 diabetic patients. *Pharmaceutical Sciences*, *20*(2), 40.

Moffatt, C. J. (2005). Identifying criteria for wound infection. European Wound Management Association.

Mogami, S., & Hattori, T. (2014). Beneficial effects of rikkunshito, a Japanese kampo medicine, on gastrointestinal dysfunction and anorexia in combination with Western drug: A systematic review. *Evidence-Based Complementary and Alternative Medicine*. doi:10.1155/2014/519035 PMID:24778703

Mohammed, H. A., & Omer, A. F. A. (2015). Antibacterial activity of *Azadirachta indica* (Neem) leaf extract against bacterial pathogens in Sudan. *American Journal of Research Communication*, *3*(5), 246–251.

Mohammed, R. K., Ibrahim, S., Atawodi, S. E., Eze, E. D., Suleiman, J. B., & Malgwi, I. S. (2012). The study of the effects of n-butanol fraction of *Alchornea cordifolia* leaf extract on lipid profile and liver enzymes in streptozotocin-induced diabetic rats. *Global Journal of Medicinal Plant Research*, *1*(1), 1–7.

Mohanapriya, M. & Ramaswamy, L. (2012). Amla- the wonder of ayurvedic medicine. *Journal of Ayurvedic and Herbal Medicine*, *2*(5), 828-834.

Mohanty, A., Pradhan, D. K., Mishra, M. R., Sahoo, J. K., Mishra, A., Nandy, B. C., & Mokade, L. (2010). Preliminary pytochemical screening and wound healing activity of *Andrographis peniculata. Journal of Chemical and Pharmaceutical Research*, *2*(4), 649–654.

Mokkhasmit, M., Swasdimongkol, K., Ngarmwathana, W., Stanley, M. P. P., Kamalakkannan, N., & Menon, V. P. (2003).. . *Journal of Ethnopharmacology*, *84*(2-3), 205–209. doi:10.1016/S0378-8741(02)00316-1 PMID:12648817

Moleyar, V., & Narasimham, P. (1986). Antifungal activity of some essential oil components. *Food Microbiology*, *3*(4), 331–336. doi:10.1016/0740-0020(86)90017-1

Mollazadeh, H., Cicero, A. F., Blesso, C. N., Pirro, M., Majeed, M., & Sahebkar, A. (2019). Immune modulation by curcumin: The role of interleukin-10. *Critical Reviews in Food Science and Nutrition*, *59*(1), 89–101. doi:10.1080/10408398.2017.1358139 PMID:28799796

Moncada, S. (1991). Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacological Reviews*, *43*, 109–142. PMID:1852778

More, P., & Pai, K. (2012). *In vitro* NADH-oxidase, NADPH-oxidase and myeloperoxidase activity of macrophages after *Tinospora cordifolia* (guduchi) treatment. *Immunopharmacology and Immunotoxicology*, *34*(3), 368–372. doi:10.3109/08923973.2011.606324 PMID:22295977

Morita, H., Tomizawa, Y., Tsuchiya, T., Hirasawa, Y., Hashimoto, T., & Asakawa, Y. (2009). Antimitotic activity of two macrocyclic bis (bibenzyls), isoplagiochins A and B from the liverwort Plagiochila fruticosa. *Bioorganic & Medicinal Chemistry Letters*, *19*(2), 493–496. doi:10.1016/j.bmcl.2008.11.036 PMID:19056262

Mou, K. M., & Dash, P. R. (2016). A comprehensive review on *Gynura procumbens* leaves. *Int J Pharmacognosy*, *3*(4), 167–174.

Mudgal, V. (1975). Studies on medicinal properties of *Convolvulus pluricaulis* and *Boerhaavia diffusa. Planta Medica*, *28*(05), 62–68. doi:10.1055-0028-1097830 PMID:1178789

Mueller, M., & Jungbauer, A. (2008). Red clover extract: A putative source for simultaneous treatment of menopausal disorders and the metabolic syndrome. *Menopause (New York, N.Y.)*, *15*(6), 1120–1131. doi:10.1097/gme.0b013e31817062ce PMID:18724264

Mukherjee, P. K., Kumar, V., Mal, M., & Houghton, P. J. (2007). *In vitro* acetylcholinesterase inhibitory activity of the essential oil from *Acorus calamus* and its main constituents. *Planta Medica*, *73*(03), 283–285. doi:10.1055-2007-967114 PMID:17286241

Mukherjee, P. K., Saha, K., Murugesan, T., Mandal, S. C., Pal, M., & Saha, B. P. (1998). Screening of anti-diarrhoeal profile of some plant extracts of a specific region of West Bengal, India. *Journal of Ethnopharmacology*, *60*(1), 85–89. doi:10.1016/S0378-8741(97)00130-X PMID:9533436

Mukherjee, P., Senapati, S., Mandal, D., Ahmad, A., Khan, M. I., Kumar, R., & Sastry, M. (2002). Extracellular synthesis of gold nanoparticles by the fungus Fusarium oxysporum. *ChemBioChem*, *3*(5), 461–463. doi:10.1002/1439-7633(20020503)3:5<461::AID-CBIC461>3.0.CO;2-X PMID:12007181

Mukherjee, R., De, U. K., & Ram, G. C. (2010). Evaluation of mammary gland immunity and therapeutic potential of *Tinospora cordifolia* against bovine subclinical mastitis. *Tropical Animal Health and Production*, *42*(4), 645–651. doi:10.100711250-009-9471-z PMID:19876755

Mulvaney, P. (1996). Surface plasmon spectroscopy of nanosized metal particles. *Langmuir*, *12*(3), 788–800. doi:10.1021/la9502711

Murad, S., Raza, H., & Bashir, A. (2010). Atherosclerosis may be prevented by using psyllium husk. *Pakistan Journal of Medical & Health Sciences*, *4*(3), 255–258.

Murata, K., Takeshita, F., Samukawa, K., Tani, T., & Matsuda, H. (2012). Effects of ginseng rhizome and ginsenoside Ro on testosterone 5α-reductase and hair re-growth in testosterone-treated mice. *Phytotherapy Research*, *26*(1), 48–53. doi:10.1002/ptr.3511 PMID:21538628

Murphy, C. J., Gole, A. M., Stone, J. W., Sisco, P. N., Alkilany, A. M., Goldsmith, E. C., & Baxter, S. C. (2008). Gold nanoparticles in biology: Beyond toxicity to cellular imaging. *Accounts of Chemical Research*, *41*(12), 1721–1730. doi:10.1021/ar800035u PMID:18712884

Musset, L., Bouchaud, O., Matheron, S., Massias, L., & Le Bras, J. (2006). Clinical atovaquone-proguanil resistance of Plasmodium falciparum associated with cytochrome b codon 268 mutations. *Microbes and Infection*, *8*(11), 2599–2604. doi:10.1016/j.micinf.2006.07.011 PMID:16962361

Nadig, P. D., Revankar, R. R., Dethe, S. M., Narayanswamy, S. B., & Aliyar, M. A. (2012). Effect of *Tinospora cordifolia* on experimental diabetic neuropathy. *Indian Journal of Pharmacology*, *44*(5), 580–583. doi:10.4103/0253-7613.100380 PMID:23112417

Nadkarni, K. M. (1976). *Indian Materia Medica* (Vol. 1). Mumbai, India: Popular Prakashan.

Nadkarni, A. N. (1989). *Hemidesmus indicus* R. *Br. Doctor KM Nadkarni's Indian Materia Medica*, *1*, 619–622.

Nadkarni, K. M. 1954. *Indian materia Medica.* Popular Prakashan.

Nadkarni, K. M., & Nadkarni, A. K. (1976). *Indian Meteria Medica* (3rd ed., Vol. 1). Popular Prakasan Pvt. Ltd Mumbai.

Nadkarni, K. M., & Nadkarni, A. K. (1999). *Indian materia medica - with ayurvedic, unani-tibbi, siddha, allopathic, homeopathic, naturopathic and home remedies* (Vol. 1). Bombay, India: Popular Prakashan Private Ltd.

Nadumane, V. K. (2011). Evaluation of the anticancer and cytotoxic potentials of *Acacia catechu* extracts in vitro. *The Journal of Pharmacy and Pharmacology*, *2*, 190–195.

Nagajyothi, P. C., Lee, K. D., & Speekanth, T. V. M. (2014). Biogenic synthesis of gold nanoparticles (uasi-spherical, triangle, and hexagonal) using *Lonicera japonica* flower extract and its antimicrobial activity. *Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry*, *44*(7), 1011–1018. doi:10.1080/15533174.2013.797456

Nagaraju, G., Chinnalalaiah, R., Nagaraju, P., & Kumar, P. A. (2012). Anti-inflammatory and anti-oxidant activities of ethanolic extract of *Euphorbia thymifolia* Linn. Whole plant. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*, 516–519.

Nagraj, B., Divya, T. K., Barasa, M., Krshnamurthy, N. B., Dinesh, R., Negrila, C. C., & Predoi, D. (2012). Phytosynthesis of gold nanoparticles using *Caesalpina pulcherrima* (peacock flower) flower extract and evaluation of their antimicrobial activities. *Digest Journal of Nanomaterials and Biostructures*, *7*, 899–905.

Nahata, A., Patil, U. K., & Dixit, V. K. (2008). Effect of *Convulvulus pluricaulis* Choisy. on learning behaviour and memory enhancement activity in rodents. *Natural Product Research*, *22*(16), 1472–1482. doi:10.1080/14786410802214199 PMID:19023811

Nahata, A., Patil, U. K., & Dixit, V. K. (2010). Effect of *Evolvulus alsinoides* Linn. on learning behavior and memory enhancement activity in rodents. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *24*(4), 486–493. PMID:19610035

Naidoo, I., & Roper, C. (2013). Mapping 'partially resistant', 'fully resistant', and 'super resistant' malaria. *Trends in Parasitology*, *29*(10), 505–515. doi:10.1016/j.pt.2013.08.002 PMID:24028889

Naik, D. G., Vaidya, H. S., & Behera, B. C. (2009). Antioxidant activity of Indian propolis. *Journal of ApiProduct and ApiMedical Science*, *1*(4), 110–120. doi:10.3896/IBRA.4.01.4.03

Naik, G. H., & Satav, J. G. (2003). Comparative antioxidant activity of individual herbal components used in Ayurvedic medicine. *Phytochemistry*, *63*(1), 97–104. doi:10.1016/S0031-9422(02)00754-9 PMID:12657303

Nail, T. N. A., Ali, M. M., & Salim, E. R. A. (2017). Phytochemical studies on sudanese rocket (*Erucasativa*) seeds and oil constituents. *Am J Phytomedicine Clin Ther*, *5*, 1.

Nair, K. P. (2019). Genetics of Turmeric. In *Turmeric (Curcuma longa L.) and Ginger (Zingiber officinale Rosc.)-World's Invaluable Medicinal Spices* (pp. 37–51). Cham: Springer.

Nair, R., Varghese, S. H., Nair, B. G., Maekawa, T., Yoshida, Y., & Kumar, D. S. (2010). Nanoparticulate material delivery to plants. *Plant Science*, *179*(3), 154–163. doi:10.1016/j.plantsci.2010.04.012

Naito, R., & Tohda, C. (2006). Characterization of anti-neurodegenerative effects of *Polygala tenuifolia* in Aβ (25-35)-treated cortical neurons. *Biological & Pharmaceutical Bulletin*, *29*(9), 1892–1896. doi:10.1248/bpb.29.1892 PMID:16946504

Narayanan, A., Raja, S., Ponmurugan, K., Kandekar, S., Natarajaseenivasan, K., Maripandi, A., & Mandeel, Q. (2011). Antibacterial activity of selected medicinal plants against multiple antibiotic resistant uropathogens: A study from Kolli Hills, Tamil Nadu, India. *Beneficial Microbes*, *2*(3), 235–243. doi:10.3920/BM2010.0033 PMID:21986363

Nasri, H. (2013). Toxicity and safety of medicinal plants. *Journal of HerbMed Pharmacology, 2*.

Nayak, B. S., & Pereira, L. M. P. (2006). *Catharanthus roseus* flower extract has wound-healing activity in Sprague Dawley rats. *BMC Complementary and Alternative Medicine*, *6*(4), 1–6. doi:10.1186/1472-6882-6-41 PMID:17184528

Nayak, B. S., Ramdeen, R., Adogwa, A., Ramsubhag, A., & Marshall, J. R. (2012). Wound-healing potential of an ethanol extract of *Carica papaya* (Caricaceae) seeds. *International Wound Journal*, *9*(6), 650–655. doi:10.1111/j.1742-481X.2011.00933.x PMID:22296524

Nayampalli, S., Ainapure, S. S., & Nadkami, P. M. (1982). Study of antiallergic acid bronchodilator effect of *Tinospora cordifolia. Indian Journal of Pharmaceutical Sciences*, *14*, 64–66.

Nayampalli, S., Ainapure, S. S., & Nadkarni, P. M. (1982). Study of antiallergic acid bronchodilator effects of *Tinospora cordifolia. The Indian Journal of Pharmacy*, *14*, 64–66.

Nazarian-Samani, Z., Sewell, R. D., Lorigooini, Z., & Rafieian-Kopaei, M. (2018). Medicinal plants with multiple effects on diabetes mellitus and its complications: A Systematic review. *Current Diabetes Reports*, *18*(10), 72. doi:10.100711892-018-1042-0 PMID:30105479

Neetu, S., Dhanila, V., Rakesh, B., Anjali, K., Ashish, J., & Sanjay, J. (2009). Development and evaluation of polyherbal formulations for hair growth activity. *Pharmacognosy Journal*, *1*(2), 165–170.

Negi, J. S., Singh, P., Joshi, G. P., Rawat, M. S., & Bisht, V. K. (2010). Chemical constituents of Asparagus. *Pharmacognosy Reviews*, *4*(8), 215. doi:10.4103/0973-7847.70921 PMID:22228964

Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F., & Walters, M. A. (2017). The essential medicinal chemistry of curcumin: Miniperspective. *Journal of Medicinal Chemistry*, *60*(5), 1620–1637. doi:10.1021/acs.jmedchem.6b00975 PMID:28074653

Newman, D. J., & Cragg, G. M. (2016). Natural products as sources of new drugs from 1981 to 2014. *Journal of Natural Products*, *79*(3), 629–661. doi:10.1021/acs.jnatprod.5b01055 PMID:26852623

Ngozi, A. O., Josephine, O. O., & Felicity, E. (2013). Anti-hyperlipidemic effect of aqueous leaf extract of *Emilia praetermissa* milne-redh (Asteraceae) in rats. *International Journal of Biosciences*, *3*(5), 68–77. doi:10.12692/ijb/3.5.68-77

Nguyen, C., Baskaran, K., Pupulin, A., Ruvinov, I., Zaitoon, O., Grewal, S., ... Pandey, S. (2019). Hibiscus flower extract selectively induces apoptosis in breast cancer cells and positively interacts with common chemotherapeutics. *BMC Complementary and Alternative Medicine*, *19*(1), 98. doi:10.118612906-019-2505-9 PMID:31060537

Niederkruger, H., Dabrowska-Schlepp, P., & Schaaf, A. (2014). Suspension culture of plant cells under phototrophic conditions. In H.P. Meyer & D.R. Schmidhalter (Ed.), Industrial Scale Suspension Culture of Living Cells. Weinheim: Wiley-VCH Verlag GmbH & Co. KGa-A. doi:10.1002/9783527683321.ch08

Nielsen, C. M., Vekemans, J., Lievens, M., Kester, K. E., Regules, J. A., & Ockenhouse, C. F. (2018). RTS, S malaria vaccine efficacy and immunogenicity during *Plasmodium falciparum* challenge is associated with HLA genotype. *Vaccine*, *36*(12), 1637–1642. doi:10.1016/j.vaccine.2018.01.069 PMID:29439870

Nikaido, H., & Pages, J. M. (2012). Broad-specificity efflux pumps and their role in multidrug resistance of Gram-negative bacteria. *FEMS Microbiology Reviews*, *36*(2), 340–363. doi:10.1111/j.1574-6976.2011.00290.x PMID:21707670

Ningombam, D. S., Devi, S. P., Singh, P. K., Pinokiyo, A., & Thongam, B. (2014). Documentation and assessment on knowledge of ethno-medicinal practitioners- a case study on local Meetei healers of Manipur. *IOSR Journal of Pharmacy and Biological Sciences*, *9*(1), 53–70. doi:10.9790/3008-09115370

Nirmala, G. A., & Pandian, K. (2007). Antibacterial efficacy of aminoglycosidic antibiotics protected gold nanoparticles-A brief study. *Colloids and Surfaces. A, Physicochemical and Engineering Aspects*, *297*(1-3), 63–70. doi:10.1016/j.colsurfa.2006.10.024

Nisha, S. N., Aysha, O. S., Rahaman, J. S. N., Kumar, P. V., Valli, S., Nirmala, P., & Reena, A. (2014). Lemon peels mediated synthesis of silver nanoparticles and its antidermatophytic activity. Spectra Acta. *A Mol. Biomol. Spectrosc.*, *124*, 194–198. doi:10.1016/j.saa.2013.12.019

Nishikimi, M., & Yagi, K. (2011). Biochemistry and molecular biology of ascorbic acid biosynthesis. In *Subcellular biochemistry* (pp. 17–39). Springer.

Nishiyama, N., Chu, P., & Saito, H. (1995). Beneficial effects of biota, a traditional Chinese herbal medicine, on learning impairment induced by basal forebrain-lesion in mice. *Biological & Pharmaceutical Bulletin*, *18*(11), 1513–1517. doi:10.1248/bpb.18.1513 PMID:8593469

Nishiyama, N., Zhou, Y., & Saito, H. (1994). Ameliorative effects of chronic treatment using DX-9386, a traditional Chinese prescription, on learning performance and lipid peroxide content in senescence accelerated mouse. *Biological & Pharmaceutical Bulletin*, *17*(11), 1481–1484. doi:10.1248/bpb.17.1481 PMID:7703968

Niu, C., Qu, J. B., & Lou, H. X. (2006). Antifungal bis [bibenzyls] from the Chinese liverwort *Marchantia polymorpha* L. *Chemistry & Biodiversity*, *3*(1), 34–40. doi:10.1002/cbdv.200690004 PMID:17193213

Nkrumah, L. J., Riegelhaupt, P. M., Moura, P., Johnson, D. J., Patel, J., Hayton, K., ... Fidock, D. A. (2009). Probing the multifactorial basis of *Plasmodium falciparum* quinine resistance: Evidence for a strain-specific contribution of the sodium-proton exchanger PfNHE. *Molecular and Biochemical Parasitology*, *165*(2), 122–131. doi:10.1016/j.molbiopara.2009.01.011 PMID:19428659

Noctor, G., Mhamdi, A., Chaouch, S., Han, Y., Neukermans, J., Marquez-Garcia, B., ... Foyer, C. H. (2012). Glutathione in plants: An integrated overview. *Plant, Cell & Environment*, *35*(2), 454–484. doi:10.1111/j.1365-3040.2011.02400.x PMID:21777251

Nur Jannah, M. H., Mahmood, A. A., Sidik, K., & Salman, I. (2006). Cytoprotective effects of honey in combination with aqueous and ethanol extracts from *Chromolaena odorata* L. (*Eupatorium odoratum* L.) in rats. *Journal of Health and Translational Medicine*, *9*(1), 7–13. doi:10.22452/jummec.vol9no1.3

Nwangwa, E. K., & Ekhoye, E. I. (2013). Anti-hyperlipidemic Activity of aqueous extracts of *Carica papaya* seeds in albino rats fed with high fat diet. *Current Trends in Technology and Science*, *II*, 2279.

Nwozo, S. O., Orojobi, B. F., & Adaramoye, O. A. (2011). Hypolipidemic and antioxidant potentials of *Xylopia aethiopica* seed extract in hypercholesterolemic rats. *Journal of Medicinal Food*, *14*(1-2), 114–119. doi:10.1089/jmf.2008.0168 PMID:21244241

Odetola, A. A., Akinloye, O., Egunjobi, C., Adekunle, W. A., & Ayoola, A. O. (2006). Possible antidiabetic and antihyperlipidaemic effect of fermented *Parkia biglobosa* (Jacq) extract in alloxan-induced diabetic rats. *Clinical and Experimental Pharmacology & Physiology*, *33*(9), 808–812. doi:10.1111/j.1440-1681.2006.04444.x PMID:16922811

Odey, M. O, Johnson, J. T, Iwara, I. A, Gauje, B, Akpan, N. S, Luke, U. O, Robert, A.E, & Ukpong, K. M. (2012). Effect of anti-hypertensive treatment with root and stem bark extracts on Nauclea latifolia on serum lipid profile. *G.J.P. and A. Sc. and Tech*., *214*, 78-84.

Ofusori, D. A., Komolafe, O. A., Adewole, O. S., Obuofor, E. M., Fakunle, J. B., & Ayoka, A. O. (2012). Effect of ethanolic leaf extract of *Croton zambesicus* (Mull arg.) on lipid profile in streptozotocin-induced diabetic rat. *Diabetologia Croatica*, 41–42.

Ojezele, M. O., & Abatan, O. M. (2011). Hypoglycaemic and coronary risk index lowering effects of Bauhinia thoningii in alloxan induced diabetic rats. *African Health Sciences*, *11*(1), 85–89. PMID:21572862

Oliver, S. J. (2013). The role of traditional medicine practice in primary health care within Aboriginal Australia: A review of the literature. *Journal of Ethnobiology and Ethnomedicine*, *9*(1), 9. doi:10.1186/1746-4269-9-46 PMID:23819729

Olsen, E. A., & Kadunce, D. P. (1997). Disorders of hair growth: Diagnosis and treatment. *Journal of the American Academy of Dermatology*, *36*(5), 804–804.

Olukunle, J. O., Abatan, M. O., Adenubi, O. T., & Amusan, T. A. (2012). Hypoglycaemic and hypolipidaemic effects of crude extracts and chromatographic fractions of *Morinda morindoides* root bark in diabetic rats. *Acta Veterinaria Brno*, *81*(3), 269–274. doi:10.2754/avb201281030269

Oluwatosin, A., Akintayo, O., Achem, J., & Fafun-so, M. A. (2008). Lipid-lowering effects of methanolic extracts of *V. amygdalina* leaves in rats fed on high cholesterol diet. *Journal of the American Medical Association*, *251*, 351–364.

Oppenheimer, A. (1937). Turmeric (curcumin) in biliary diseases. *Lancet*, *229*(5924), 619–621. doi:10.1016/S0140-6736(00)98193-5

Orellana-Escobedo, L., Rosales-Mendoza, S., Romero-Maldonado, A., Parsons, J., Decker, E. L., Monreal-Escalante, E., ... Reski, R. (2015). An Env-derived multi-epitope HIV chimeric protein produced in the moss *Physcomitrella patens* is immunogenic in mice. *Plant Cell Reports*, *34*(3), 425–433. doi:10.100700299-014-1720-6 PMID:25477207

Orhue, N. E. J., & Nwanze, E. A. C. (2006). *Scoparia dulcis* reduces the severity of trypanosome brucei-induced hyperlipidaemia in the rabbit. *African Journal of Biotechnology*, *5*, 883–887.

Oyewole & Akingbala. (2011). Phytochemical analysis and hypolipidemic properties of *Jatropha tanjorensis* leaf extract. *Eur. Journal of Med. Plants*, (4), 180-185.

Oyewole, O. A., & Abalaka, M. E. (2012). Antimicrobial activities of *Telfairia occidentalis* (fluted pumpkins) leaf extract against selected intestinal pathogens. *Journal of Health Sciences (Sarajevo)*, *2*, 1–4.

Öztürk, M., Aydoğmuş-Öztürk, F., Duru, M. E., & Topçu, G. (2007). Antioxidant activity of stem and root extracts of Rhubarb (*Rheum ribes*): An edible medicinal plant. *Food Chemistry*, *103*(2), 623–630. doi:10.1016/j.foodchem.2006.09.005

Padayatty, S. J., Katz, A., Wang, Y., Eck, P., Kwon, O., Lee, J. H., & Levine, M. (2003). Vitamin C as an antioxidant: Evaluation of its role in disease prevention. *Journal of the American College of Nutrition*, *22*(1), 18–35. doi:10.1080/07315724.2003.10719272 PMID:12569111

Padua de, L.S., Bunyapraphatsara, N., & Lemmens, R.H.M.J. (1999). Plant resources of South-East Asia, No 12(1). Medicinal and Poisonous Plant 1. Backhuys Publishers.

Paguigan, N. D., Castillo, D. H. B., & Chichioco-Hernandez, C. L. (2014). Anti-ulcer activity of leguminosae plants. *Arquivos de Gastroenterologia*, *51*(1), 64–68. doi:10.1590/S0004-28032014000100013 PMID:24760067

Pak, M. E., Kim, Y. R., Kim, H. N., Ahn, S. M., Shin, H. K., Baek, J. U., & Choi, B. T. (2016). Studies on medicinal herbs for cognitive enhancement based on the text mining of Dongeuibogam and preliminary evaluation of its effects. *Journal of Ethnopharmacology*, *179*, 383–390. doi:10.1016/j.jep.2016.01.006 PMID:26773844

Pallavi, G., Gupta, V., & Rishi, R. (2011). Ethnopharmaco–botanical review of padmaka–prunus puddum roxb. *International Journal of Ayurvedic And Herbal Medicine*, *1*(3), 87–99.

Pallavi, R., Elakkiya, S., Tennety, S. S. R., & Devi, P. S. (2012). Anthocyanin analysis and its anticancer property from sugar cane (*Saccharum officinarum*) peel. *International Journal of Research in Pharmacy and Chemistry*, *2*(2), 338–345.

Panda, B. R., Mohanta, S. R., Manna, A. K., & Si, S. (2011). *In vitro* antioxidant activity on the aerial parts of *Cocculus hirsutus* Diels. *Journal of Advanced Pharmaceutical Research*, *2*, 18–23.

Pandey, A., & Shweta. (2011). Antibacterial properties of *Psidium guajava* leaves, fruits and stems against various pathogens. *Int. J. Pharm. Res. Dev*, *3*, 15–24.

Pandey, A., & Singh, P. (2011). Antibacterial activity of *Syzygium aromaticum* (clove) with metal ion effect against food borne pathogens. *Asian J. Plant Sci. Res*, *1*, 69–80.

Pandey, M., & Khan, A. (2002). Hypoglycaemic effect of defatted seeds and water soluble fibre from the seeds of *Syzygium cumini* (Linn.) skeels in alloxan diabetic rats. *Indian Journal of Experimental Biology*, *40*(10), 1178–1182. PMID:12693701

Pandey, S., & Alam, A. (2016). *Marchantia polymorpha* L.: An emerging model plant system to study contemporary plant biology – A Review. *Plant Science Today*, *3*(2), 88–99. doi:10.14719/pst.2016.3.2.221

Panduraju, T., Parvathi, B., Rammohan, M., & Reddy, C. S. (2011). Wound healing properties of *Cleome viscosa* Linn. *Hygeia JD Med*, *3*(1), 41–45.

Pandurangan, A. K., & Mustafa, M. R. (2018). Anticancer Plants: Natural Products and Biotechnological Implements. In The therapeutic strategies of natural agents on Triple-negative breast cancer. Springer International Publishing.

Pandurangan, A. K., Kanagesan, S., Narayanaswamy, R., Esa, N. M., & Padmanabhan, P. (2015). *Applications of NanoBioMaterials: Nanobiomaterials in Cancer Therapy.* In A. M. Grumezescu (Ed.), *NanoBioMaterials based delivery of drugs in various cancer therapies: Classifying the mechanisms of action (using Biochemical and Molecular biomarkers)* (Vol. 7, pp. 331–365). Elsevier Publisher.

Pankaj, K. S., & Subir, K. (2013). Biosynthesis of elixir of life (gold nanoparticles) from plants. *Journal of Environmental Nanotechnology*, *2*, 52–62.

Pantoja, C. V., Martín, N. T., Norris, B. C., & Contreras, C. M. (2000). Purification and bioassays of a Diuretic and natriuretic fraction from garlic (*Allium sativum*). *Journal of Ethnopharmacology*, *70*(1), 35–40. doi:10.1016/S0378-8741(99)00145-2 PMID:10720787

Paolini, J., Costa, J., & Bernardini, A. F. (2005). Analysis of the essential oil from aerial parts of *Eupatorium cannabinum* subsp. *corsicum* (L.) by gas chromatography with electron impact and chemical ionization mass spectrometry. *Journal of Chromatography. A*, *1076*(1-2), 170–178. doi:10.1016/j.chroma.2005.03.131 PMID:15974084

Paolini, J., Costa, J., & Bernardini, A. F. (2007). Analysis of the essential oil from the roots of *Eupatorium cannabinum* subsp. corsicum (L.) by GC, GC-MS and 13C-NMR. *Phytochemical Analysis*, *18*(3), 235–244. doi:10.1002/pca.977 PMID:17500367

Parasuraman, S., Thing, G. S., & Dhanaraj, S. A. (2014). Polyherbal formation: Concept of Ayurveda. *Pharmacognosy Reviews*, *8*(16), 73–80. doi:10.4103/0973-7847.134229 PMID:25125878

Parente, L. M. L., Júnior, L., de Souza, R., Tresvenzol, L. M. F., Vinaud, M. C., de Paula, J. R., & Paulo, N. M. (2011). Wound healing and anti-inflammatory effect in animal models of *Calendula officinalis* L. growing in Brazil. *Evidence-Based Complementary and Alternative Medicine*, 1–7. PMID:22315631

Parichatikanond, W., Suthisisang, C., Dhepakson, P., & Herunsalee, A. (2010). Study of anti-inflammatory activities of the pure compounds from *Andrographis paniculata* (Burm.f.) Nees and their effects on gene expression. *International Immunopharmacology*, *10*(11), 1361–1373. doi:10.1016/j.intimp.2010.08.002 PMID:20728594

Parija, S. P., & Praharaj, I. (2011). Drug resistance in malaria. *Indian Journal of Medical Microbiology*, *29*(3), 243–248. doi:10.4103/0255-0857.83906 PMID:21860103

Park, B., Prasad, S., Yadav, V., Sung, B., & Aggarwal, B. B. (2011). Boswellic acid suppresses growth and metastasis of human pancreatic tumors in an orthotopic nude mouse model through modulation of multiple targets. *PLoS One*, *6*(10), e26943. doi:10.1371/journal.pone.0026943 PMID:22066019

Park, C. H., Choi, S. H., Koo, J. W., Seo, J. H., Kim, H. S., Jeong, S. J., & Suh, Y. H. (2002). Novel cognitive improving and neuroprotective activities of *Polygala tenuifolia* Willdenow extract, BT-11. *Journal of Neuroscience Research*, *70*(3), 484–492. doi:10.1002/jnr.10429 PMID:12391609

Parker, J. S., Mullins, M., Cheang, M. C. U., Leung, S., Voduc, D., Vickery, T., ... Bernard, P. S. (2009). Supervised risk predictor of breast cancer based on intrinsic subtypes. *Journal of Clinical Oncology*, *27*(8), 1160–1167. doi:10.1200/JCO.2008.18.1370 PMID:19204204

Park, H. J., Kim, S. H., Kim, H. J., & Choi, S. H. (2007). A new composition of nanosized silica-silver for control of various plant diseases. *Plant Pathology*, *22*(3), 295–320. doi:10.5423/PPJ.2006.22.3.295

Parsons, J., Altmann, F., Arrenberg, C. K., Koprivova, A., Beike, A. K., Stemmer, C., ... Decker, E. L. (2012). Moss-based production of asialo-erythropoietin devoid of Lewis A and other plant-typical carbohydrate determinants. *Plant Biotechnology Journal*, *10*(7), 851–861. doi:10.1111/j.1467-7652.2012.00704.x PMID:22621344

Partha, P., & Hossain, A. E. (2007). Ethnobotanical investigation into the Mandi ethnic community in Bangladesh. *Bangladesh Journal of Plant Taxonomy*, *14*(2), 129–145. doi:10.3329/bjpt.v14i2.532

Patel, A., Bigoniya, P., Singh, C. S., & Patel, N. S. (2013). Radioprotective and cytoprotective activity of *Tinospora cordifolia* stem enriched extract containing cordifolioside-A. *Indian Journal of Pharmacology*, *45*(3), 237–243. doi:10.4103/0253-7613.111919 PMID:23833365

Patel, M. B., & Mishra, S. (2011). Hypoglycemic activity of alkaloidal fraction of *Tinospora cordifolia*. *Phytomedicine*, *18*(12), 1045–1052. doi:10.1016/j.phymed.2011.05.006 PMID:21665451

Patel, S., Sharma, V. S., Chauhan, N., Thakur, M., & Dixit, V. K. (2015). Hair growth: Focus on herbal therapeutic agent. *Current Drug Discovery Technologies*, *12*(1), 21–42. doi:10.2174/1570163812666150610115055 PMID:26058803

Patel, U., Kulkarni, M., Undale, V., & Bhosale, A. (2009). Evaluation of diuretic activity of aqueous and methanol extracts of *Lepidium sativum* Garden Cress (Cruciferae) in Rats. *Tropical Journal of Pharmaceutical Research*, *8*(3), 215–219. doi:10.4314/tjpr.v8i3.44536

Patgiri, B., Umretia, B. L., Vaishnav, P. U., Prajapati, P. K., Shukla, V. J., & Ravishankar, B. (2014). Anti-inflammatory activity of guduchi ghana (aqueous extract of *Tinospora cordifolia* Miers.). *Ayu*, *35*(1), 108–110. doi:10.4103/0974-8520.141958 PMID:25364210

Patridge, E., Gareiss, P., Kinch, M. S., & Hoyer, D. (2016). An analysis of FDA-approved drugs: Natural products and their derivatives. *Drug Discovery Today*, *21*(2), 204–207. doi:10.1016/j.drudis.2015.01.009 PMID:25617672

Pattanaik, B., & Lindberg, P. (2015). Terpenoids and their biosynthesis in cyanobacteria. *Life (Chicago, Ill.)*, *5*(1), 269–293. PMID:25615610

Pattanayak, P., Behra, P., Das, D., & Panda, S. K. (2010). *Ocimum sanctum* Linn. A reservoir plant for therapeutic applications:An overview. *Pharmacognosy Reviews*, *4*(7), 95–105. doi:10.4103/0973-7847.65323 PMID:22228948

Pattanayak, S. P., & Sunita, P. (2008). Wound healing, anti-microbial and antioxidant potential of *Dendrophthoe falcata* (Lf) Ettingsh. *Journal of Ethnopharmacology*, *120*(2), 241–247. doi:10.1016/j.jep.2008.08.019 PMID:18790035

Patwardhan, B., Warude, D., Pushpangadan, P., & Bhatt, N. (2005). Ayurveda and traditional Chinese medicine: A comparative overview. *Evidence-Based Complementary and Alternative Medicine*, *2*(4), 465–473. doi:10.1093/ecam/neh140 PMID:16322803

Paul, D., De, D., Ali, K. M., Chatterjee, K., Nandi, D. K., & Ghosh, D. (2010). Comparative study on the spermicidal activity of organic solvent fractions from hydroethanolic extracts of *Achyranthes aspera* and *Stephania hernandifolia* in human and rat sperm. *Contraception*, *81*(4), 355–361. doi:10.1016/j.contraception.2009.09.001 PMID:20227555

Pavanand, K., Yongvanitchit, K., Webster, H. K., Dechatiwongse, T., Nutakul, W., Jewvachdamrongkul, Y., & Bansiddhi, J. (1988). *In vitro* antimalarial activity of a Thai medicinal plant *Picrasma javanica* Bl. *Phytotherapy Research*, *2*(1), 33–36. doi:10.1002/ptr.2650020105

Payton, F., Sandusky, P., & Alworth, W. L. (2007). NMR study of the solution structure of curcumin. *Journal of Natural Products*, *70*(2), 143–146. doi:10.1021/np060263s PMID:17315954

Pearson, V. E. (2001). Galantamine: A new Alzheimer drug with a past life. *The Annals of Pharmacotherapy*, *35*(11), 1406–1413. doi:10.1345/aph.1A092 PMID:11724094

Pekmezci, E., Dundar, C., & Turkoglu, M. (2018). Proprietary herbal extract downregulates the gene expression of IL-1α in HaCaT cells: Possible implications against nonscarring alopecia. *Medicinski Arhiv*, *72*(2), 136. doi:10.5455/medarh.2018.72.136-140 PMID:30302033

Pereira, R. P., Fachinetto, R., de Souza Prestes, A., Puntel, R. L., Santos da Silva, G. N., Heinzmann, B. M., ... Rocha, J. B. T. (2009). Antioxidant effects of different extracts from *Melissa officinalis, Matricaria recutita* and *Cymbopogon citratus. Neurochemical Research*, *34*(5), 973–983. doi:10.100711064-008-9861-z PMID:18853256

Perera, B.P.R. (2014). A study on the plants used as Chopachini. *Journal of Homeopathy and Ayurvedic Medicine*, *3*, 170.

Perez-Gutierrez, R. M., & Damian-Guzman, M. M. (2012). A potent a-glucosidase and a-amylase inhibitor isolated from *Azadirachta indica* leaves and in vivo antidiabetic property in streptozotocin-nicotinamide-induced type 2 diabetes in mice. *Biological & Pharmaceutical Bulletin*, *35*, 1516–1524. doi:10.1248/bpb.b12-00246 PMID:22975503

Philip, D., Unni, C., Aromal, S. A., & Vidhu, V. K. (2011). *Murraya Koenigii* leaf-assisted rapid green synthesis of silver and gold nanoparticles. *Spectrochimica Acta. Part A: Molecular Spectroscopy*, *78*(2), 899–904. doi:10.1016/j.saa.2010.12.060 PMID:21215687

Phyo, A. P., Nkhoma, S., Stepniewska, K., Ashley, E. A., Nair, S., McGready, R., ... Nosten, F. (2012). Emergence of artemisinin-resistant malaria on the western border of Thailand: A longitudinal study. *Lancet*, *379*(9830), 1960–1966. doi:10.1016/S0140-6736(12)60484-X PMID:22484134

Pietta, P. G. (2000). Flavonoids as antioxidants. *Journal of Natural Products*, *63*(7), 1035–1042. doi:10.1021/np9904509 PMID:10924197

Pilarski, R., Zieliński, H., Ciesiołka, D., & Gulewicz, K. (2006). Antioxidant activity of ethanolic and aqueous extracts of *Uncaria tomentosa* (Willd.) DC. *Journal of Ethnopharmacology*, *104*(1-2), 18–23. doi:10.1016/j.jep.2005.08.046 PMID:16202551

Pillai, N. R., & Santhakumari, G. (1984). Toxicity studies on nimbidin, a potential anti-ulcer drug. *Planta Medica*, *50*(2), 146–148. doi:10.1055-2007-969655 PMID:6473547

Polívková, Z., Šmerák, P., Demová, H., & Houška, M. (2010). Antimutagenic effects of lycopene and tomato purée. *Journal of Medicinal Food*, *13*(6), 1443–1450. doi:10.1089/jmf.2009.0277 PMID:20874227

Poltanov, E. A., Shikov, A. N., Dorman, H. J. D., Pozharitskaya, O. N., Makarov, V. G., Tikhonov, V. P., & Hiltunen, R. (2009). Chemical and antioxidant evaluation of Indian gooseberry (*Emblica officinalis* Gaertn., syn. *Phyllanthus emblica* L.) supplements. *Phytotherapy Research*, *23*(9), 1309–1315. doi:10.1002/ptr.2775 PMID:19172666

Postic, C., Dentin, R., & Girard, J. (2004). Role of the liver in the control of carbohydrate and lipid homeostasis. *Diabetes & Metabolism*, *30*(5), 398–408. doi:10.1016/S1262-3636(07)70133-7 PMID:15671906

Prajapati, N. D. (2003). *Handbook of Medicinal Plants: A Complete Source*. Agrobios.

Prakash, P., & Gupta, N. (2005). Therapeutic uses of *Ocimum sanctum* Linn (Tulsi) with a note on eugenol and its pharmacological actions: A short review. *Indian Journal of Physiology and Pharmacology*, *49*(2), 125–131. PMID:16170979

Prasad, K., & Bisht, G. (2011). Evaluation of nutritive minerals and antioxidants values of *Euphorbia thymifolia* Linn. *Current Research in Chemistry*, *3*(2), 98–105. doi:10.3923/crc.2011.98.105

Pratt, D. E. (1992). *Natural antioxidants from plant material*. Academic Press.

Preeti, S. (2011). *Tinospora cordifolia* (Amrita)-a miracle herb and lifeline too many diseases. *International Journal of Medicinal and Aromatic Plants*, *1*(2), 57–61.

Prince, P.S., Menon, V.P., & Pari, L. (1998). Hypoglycaemic activity of *Syzigium cumini* seeds: effect on lipid peroxidation in alloxan diabetic rats. *Journal of Ethnopharmacology, 61*(1), 1-7.

Pringle, J. C., Carpi, G., Almagro-Garcia, J., Zhu, S. J., Kobayashi, T., Mulenga, M., & Norris, D. E. (2018). RTS, S/AS01 malaria vaccine mismatch observed among *Plasmodium falciparum* isolates from southern and central Africa and globally. *Scientific Reports*, *8*(1), 1–8. doi:10.103841598-018-24585-8 PMID:29700348

Priyadarshini, E., Pradhan, N., Sukla, L. B., & Panda, P. K. (2014). Controlled synthesis of gold nanoparticles using *Aspergillus terreus* IF0 and its antibacterial potential against gram negative pathogenic bacteria. *Journal of Nanotechnology*, *2014*, 1–9. doi:10.1155/2014/653198

Pucci, M. J., & Dougherty, T. J. (2002). Direct quantitation of the numbers of individual penicillin-binding proteins per cell in *Staphylococcus aureus. Journal of Bacteriology*, *184*(2), 588–591. doi:10.1128/JB.184.2.588-591.2002 PMID:11751840

Pungle, P., Banavalikar, M., Suthar, A., Biyani, M., & Mengi, S. (2003). Immunomodulatory activity of boswellic acids of *Boswellia serrata* Roxb. *Indian Journal of Experimental Biology*, *14*(12), 460–462. PMID:15320503

Purandare, H., & Supe, A. (2007). Immunomodulatory role of *Tinospora cordifolia* as an adjuvant in surgical treatment of diabetic foot ulcers: A prospective randomized controlled study. *Indian Journal of Medical Sciences*, *61*(6), 347–355. doi:10.4103/0019-5359.32682 PMID:17558098

Purcaru, T., Alecu, A., Diguta, C., & Matei, F. (2015). *In vitro* evaluation of *Eupatorium cannabium* antimicrobial activity. *AgroLife Scientific Journal*, *4*(2), 92–97.

Puri, D., & Baral, N. (1998). Hypoglycemic effect of *Biophytum sensitivum* in the alloxan diabetic rabbits. *Indian Journal of Physiology and Pharmacology*, *42*, 401–406. PMID:9741656

Purohit, P., & Bohra, A. (1998). Effect of some plants extracts on conidial germination of some important phytopathogenic fungi. *Geobios*, *17*, 183–184.

Purwal, L., Gupta, S. P. B. N., & Pande, S. M. (2008). Development and evaluation of herbal formulations for hair growth. *Journal of Chemistry*, *5*(1), 34–38.

Putri, P. E., Mangisah, I., & Suthama, N. (2018). The effect of dietary supplementation of onion and garlic husk powder on protein. *Cholesterol and Fat of Duck Meat.*

Pu, W. L., Bai, R. Y., Zhou, K., Peng, Y. F., Zhang, M. Y., Hottiger, M. O., ... Sun, L. K. (2019). Baicalein attenuates pancreatic inflammatory injury through regulating MAPK, STAT3 and NF-κB activation. *International Immunopharmacology*, *72*, 204–210. doi:10.1016/j.intimp.2019.04.018 PMID:30999210

Qi, F. H., Wang, Z. X., Cai, P. P., Zhao, L., Gao, J. J., Kokudo, N., ... Tang, W. (2013). Traditional Chinese medicine and related active compounds: A review of their role on hepatitis B virus infection. *Journal of Drug Discovery and Therapeutics*, *7*, 212–224. PMID:24423652

Qinghe, G., Guangyu, L., Xiaobin, L., & Qingsong, H. (2019). Baicalein exerts a protective role in pneumonia caused by *Streptococcus pneumoniae. Frontiers in Bioscience*, *24*(5), 849–858. doi:10.2741/4755 PMID:30844717

Quigley, B. J. Jr, & Kowall, N. W. (1991). Substance P-like immunoreactive neurons are depleted in Alzheimer's disease cerebral cortex. *Neuroscience*, *41*(1), 41–60. doi:10.1016/0306-4522(91)90199-X PMID:1711654

Qu, J., Xie, C., Guo, H., Yu, W., & Lou, H. (2007). Antifungal dibenzofuran bis (bibenzyl) from the liverwort *Asterella angusta. Phytochemistry*, *68*(13), 1767–1774. doi:10.1016/j.phytochem.2007.04.036 PMID:17570447

Qurishi, Y., Hamid, A., Zargar, M. A., Singh, S. K., & Saxena, A. K. (2010). Potential role of natural molecules in health and disease: Importance of boswellic acid. *Journal of Medicinal Plants Research*, *4*(25), 2778–2786.

Radhika, B., Nasreen, B., Srisailam, K., & Reddy, V. M. (2010). Diuretic activity of *Bixa orellana* Linn. leaf extracts. *Indian Journal of Natural Products and Resources*, *1*, 353–355.

Ragasa, C. Y., Martinez, A., Chua, J. E. Y., & Rideout, J. A. (2007). A triterpene from *Musa errans. Philippine Journal of Science*, *136*(2), 167–171.

Raghunathan, K., & Mitra, M. K. (2000). *Pharmacognosy of indigenous drugs*. New Delhi, India: Central Council of Research in Ayurveda and Siddhs.

Rahier, J., Guiot, Y., Goebbels, R. M., Sempoux, C., & Henquin, J. C. (2008). Pancreatic β-cell mass in European subjects with type 2 diabetes. *Diabetes, Obesity & Metabolism*, *10*, 32–42. doi:10.1111/j.1463-1326.2008.00969.x PMID:18834431

Rahimi, R., Shams-Ardekani, M. R., & Abdollahi, M. (2010). A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease. *World Journal of Gastroenterology*, *16*(36), 4504. doi:10.3748/wjg.v16.i36.4504 PMID:20857519

Rahman, H., Shaik, H. A., Madhavi, P., & Eswaraiah, M. C. (2011). A review: Pharmacognostics and pharmacological profiles of *Nardastachys jatamansi* DC. *Elixir Pharmacy*, *39*, 5017–5020.

Rahmatullah, M., Hasan, S. K., Ali, Z., Rahman, S., & Jahan, R. (2012). Antihyperglycemic and antinociceptive activities of methanolic extract of *Euphorbia thymifolia* L. whole plants. *Journal of Chinese Integrative Medicine*, *10*(2), 228–232. doi:10.3736/jcim20120213 PMID:22313890

Rai, A., Prabune, A., & Perry, C. C. (2010). Antibiotic mediated synthesis of gold nanoparticles with potent antimicrobial activity and their application in antimicrobial coatings. *Journal of Materials Chemistry*, *20*(32), 6789–6798. doi:10.1039/c0jm00817f

Rai, D., Kumari, G., Singh, A., & Singh, K. (2013). Curcuminbioconjugates: Studies on structure-activity relationship and antibacterial properties against clinically isolated strains. *Medicinal Chemistry (Shariqah, United Arab Emirates)*, *9*(7), 999–1005. doi:10.2174/1573406411309070014 PMID:23189999

Rai, K. S., Murthy, K. D., Karanth, K. S., Nalini, K., Rao, M. S., & Srinivasan, K. K. (2002). *Clitoria ternatea* root extract enhances acetylcholine content in rat hippocampus. *Fitoterapia*, *73*(7-8), 685–689. doi:10.1016/S0367-326X(02)00249-6 PMID:12490229

Raja, A. F., Ali, F., Khan, I. A., Shawl, A. S., & Arora, D. S. (2011). Acetyl-11-keto-β-boswellic acid (AKBA); targeting oral cavity pathogens. *BMC Research Notes*, *4*(1), 406. doi:10.1186/1756-0500-4-406 PMID:21992439

Raja, A. F., Ali, F., Khan, I. A., Shawl, A. S., Arora, D. S., Shah, B. A., & Taneja, S. C. (2011). Antistaphylococcal and biofilm inhibitory activities of acetyl-11-keto-β-boswellic acid from *Boswellia serrata*. *BMC Microbiology*, *11*(1), 54. doi:10.1186/1471-2180-11-54 PMID:21406118

Rajakrishnan, V., Viswanathan, P., Rajasekharan, K. N., & Menon, V. P. (1999). Neuroprotective role of curcumin from *Curcuma longa* on ethanol-induced brain damage. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *13*(7), 571–574. doi:10.1002/(SICI)1099-1573(199911)13:7<571::AID-PTR494>3.0.CO;2-7 PMID:10548748

Rajasekaran, M., Bapna, J. S., Lakshmanan, S., Nair, A. R., Veliath, A. J., & Panchanadam, M. (1988). Antifertility effect in male rats of oleanolic acid, a triterpene from *Eugenia jambolana* flowers. *Journal of Ethnopharmacology*, *24*(1), 115–121. doi:10.1016/0378-8741(88)90142-0 PMID:3199836

Rajeshkumar, S., Malarkodi, C., Gnanajobitha, G., Paulkumar, K., Vanaja, M., Kannan, C., & Annadurai, G. (2013). Seaweed-mediated synthesis of gold nanoparticles using *Turbinaria conoides* and its characterization. *Journal of Nanostructure in Chemistry*, *3*(1), 44. doi:10.1186/2193-8865-3-44

Rajeshkumar, S., Malarkodi, C., Vanaja, M., Gnanajobitha, G., Paulkumar, K., Kannan, C., & Annadurai, G. (2013). Antibacterial activity of algae mediated synthesis of gold nanoparticles from Turbinatia conoides. *Der Pharma Chemica*, *5*, 224–229.

Rajeswari, R., Umadevi, M., Rahale, C. S., Pushpa, R., Selvavenkadesh, S., & Kumar, K. P. S. D., & Bhowmik, D. (2012). *Aloe vera:* The miracle plant its medicinal and traditional uses in India. *Journal of Pharmacognosy and Phytochemistry*, *1*(4), 118–124.

Rajkumari, S., & Sanatombi, K. (2017). Nutritional value, phytochemical composition, and biological activities of edible Curcuma species: A review. *International Journal of Food Properties, 20*(sup3), S2668-S2687.

Rajput, M., & Navneet. (2019). Antimicrobial potential of *Hydnocarpus laurifolia* seeds utilized in folkloric medicine: A possible alternative in the treatment of scalp infections. *The Pharma Innovation Journal*, *8*(1), 1–5.

Rakhi, M., Braja, G. B., & Nabasmita, M. (2013). *Acacia nilotica* (babool) leaf extract mediated size-controlled rapid synthesis of gold nanoparticles and study of its catalytic activity. *International Nano Letters*, *3*(1), 53–58. doi:10.1186/2228-5326-3-53

Ramadan, G., Al-Kahtani, M. A., & El-Sayed, W. M. (2011). Anti-inflammatory and anti-oxidant properties of *Curcuma longa* (turmeric) versus *Zingiber officinale* (ginger) rhizomes in rat adjuvant-induced arthritis. *Inflammation*, *34*(4), 291–301. doi:10.100710753-010-9278-0 PMID:21120596

Ramalakshmi, K., Rahath Kubra, I., & Jagan Mohan Rao, L. (2008). Antioxidant potential of low-grade coffee beans. *Food Research International*, *41*(1), 96–103. doi:10.1016/j.foodres.2007.10.003

Ramalingam, M., & Kim, S.-J. (2015). Phytochemical, toxicological and pharmacological studies of *Asiasari Radix*: A Review. *Tropical Journal of Pharmaceutical Research*, *14*(3), 545–554. doi:10.4314/tjpr.v14i3.26

Ramirez, R.O., & Roa Jr, C.C. (2003). The gastroprotective effect of tannins extracted from duhat (*Syzygium cumini* Skeels) bark on HCl/ethanol induced gastric mucosal injury in Sprague-Dawley rats. *Clinical Hemorheology and Microcirculation, 29*(3-4), 253-261.

Ramırez-Tortosa, M. C., Mesa, M. D., Aguilera, M. C., Quiles, J. L., Baro, L., Ramirez-Tortosa, C. L., & Gil, A. (1999). Oral administration of a turmeric extract inhibits LDL oxidation and has hypocholesterolemic effects in rabbits with experimental atherosclerosis. *Atherosclerosis*, *147*(2), 371–378. doi:10.1016/S0021-9150(99)00207-5 PMID:10559523

Ramsamy, Y., Essack, S. Y., Sartorius, B., Patel, M., & Mlisana, K. P. (2018). Antibiotic resistance trends of ESKAPE pathogens in Kwazulu-Natal, South Africa: A five-year retrospective analysis. *African Journal of Laboratory Medicine*, *7*(2), 887. doi:10.4102/ajlm.v7i2.887 PMID:30568908

Ramya, R., Anudeepa, J., Senthilkumar, C., Rajendran, S. S., Sivasakthi, R., Moorthy, C., & Venkatnarayanan, D. R. (2011). Wound healing activity of *Dodonea viscosa* Linn ointment in rats. *International Journal of Research in Pharmacy and Chemistry*, *1*(3), 481–483.

Rana, N. S., & Joshi, M. N. (1992). Investigation on the antiviral activity of ethanolic extracts of *Sysygium* sp. *Fitoterapia*, *63*, 542–544.

Randall, V. A., & Ebling, F. J. G. (1991). Seasonal changes in human hair growth. *British Journal of Dermatology*, *124*(2), 146–151. doi:10.1111/j.1365-2133.1991.tb00423.x PMID:2003996

Randhir, R., Lin, Y. T., & Shetty, K. (2004). Phenolics, their antioxidant and antimicrobial activity in dark germinated fenugreek sprouts in response to peptide and phytochemical elicitors. *Asia Pacific Journal of Clinical Nutrition*, *13*(3), 295–307. PMID:15331344

Rangama, B. N. L. D., Abayasekara, C. L., Panagoda, G. J., & Senanayake, M. R. D. M. (2009). Antimicrobial activity of *Tephrosia purpurea* (Linn.) Pers. and *Mimusops elengi* (Linn.) against some clinical bacterial isolates. *J. Natn. Sci. Found. Sri Lan*, *37*(2), 139–145. doi:10.4038/jnsfsr.v37i2.1071

Rani, S., Rahman, K., & Idris, M. (2018). Ethnomedicinal, pharmacological and phytochemical screening of supari (*Areca catechu* Linn.): A review. *Research & Reviews. Journal de Pharmacologie*, *8*(1), 6–20.

Rao, A. V., & Balachandran, B. (2002). Role of oxidative stress and antioxidants in neurodegenerative diseases. *Nutritional Neuroscience*, *5*(5), 291–309. doi:10.1080/1028415021000033767 PMID:12385592

Rao, P. R., Kumar, V. K., Viswanath, R. K., & Subbaraju, G. V. (2005). Cardioprotective activity of alcoholic extract of *Tinospora cordifolia* in ischemia-reperfusion induced myocardial infarction in rats. *Biological & Pharmaceutical Bulletin*, *28*(12), 2319–2322. doi:10.1248/bpb.28.2319 PMID:16327173

Rapp, C. (2007). *Clove as effective as topical anesthetic*. Herbal Gram.

Rasik, A. M., Raghubir, R., Gupta, A., Shukla, A., Dubey, M. P., Srivastava, S., & Kulshrestha, D. K. (1999). Healing potential of *Calotropis procera* on dermal wounds in Guinea pigs. *Journal of Ethnopharmacology*, *68*(1), 261–266. doi:10.1016/S0378-8741(99)00118-X PMID:10624886

Raskin, P., Ganda, O. P., Schwartz, S., Willard, D., Rosenstock, J., Lodewick, P. A., & McGovern, M. E. (1995). Efficacy and safety of pravastatin in the treatment of patients with type I or type II diabetes mellitus and hypercholesterolemia. *The American Journal of Medicine*, *99*(4), 362–369. doi:10.1016/S0002-9343(99)80182-X PMID:7573090

Rassias, D. J., & Weathers, P. J. (2019). Dried leaf *Artemisia annua* efficacy against non-small cell lung cancer. *Phytomedicine*, *52*, 247–253. doi:10.1016/j.phymed.2018.09.167 PMID:30599905

Rathinamoorthy, R., & Thilagavathi, G. (2014). *Terminalia chebula*-Review on Pharmacological and Biochemical Studies. *International Journal of Pharm Tech Research*, *6*(1), 97–116.

Rathnayake, D., & Sinclair, R. (2010). Male androgenetic alopecia. *Expert Opinion on Pharmacotherapy*, *11*(8), 1295–1304. doi:10.1517/14656561003752730 PMID:20426708

Ravi, K., Rajasekara, S., & Subramanian, S. (2005). Anti-hyperlipidemic effect of *Eugenia jambolana* seed kernel on streptozotocin-induced diabetes in rats. *Food and Chemical Toxicology*, *43*(9), 1433–1439. doi:10.1016/j.fct.2005.04.004 PMID:15964674

Ravi, K., Ramachandran, B., & Subramanian, S. (2004). Effect of *Eugenia jambolana* seed kernel on antioxidant defense system in streptozotocin-induced diabetes in rats. *Life Sciences*, *75*(22), 2717–2731. doi:10.1016/j.lfs.2004.08.005 PMID:15369706

Ravindran, A., Chandran, P., & Khan, S. S. (2013). Biofunctionalized silver nanoparticles: Advances and prospects. *Colloids and Surfaces. B, Biointerfaces*, *105*, 342–352. doi:10.1016/j.colsurfb.2012.07.036 PMID:23411404

Ravindran, P. N., Babu, K. N., & Sivaraman, K. (2007). *Turmeric: the genus Curcuma*. CRC press.

Reddy, B. K., Gowda, S., & Arora, A. K. (2011). Study of wound healing activity of aqueous and alcoholic bark extracts of *Acacia catechu* on rats. *Journal of Pharmaceutical Sciences*, *1*(3), 220–225.

Rekha, N., Balaji, R., & Deecaraman, M. (2008). Effect of aqueous extract of *Syzygium cumini* pulp on anti-oxidant defense system in streptozotocin induced diabetic rats. *Ir. J Pharmacol Ther*, *7*, 137–145.

Rencz, F., Péntek, M., Bortlik, M., Zagorowicz, E., Hlavaty, T., Śliwczyński, A., ... Lakatos, P. L. (2015). Biological therapy in inflammatory bowel diseases: Access in Central and Eastern Europe. *World Journal of Gastroenterology: WJG*, *21*(6), 17–28. doi:10.3748/wjg.v21.i6.1728 PMID:25684937

Rensing, S. A., Ick, J., Fawcett, J. A., Lang, D., Zimmer, A., Van de Peer, Y., & Reski, R. (2007). An ancient genome duplication contributed to the abundance of metabolic genes in the moss *Physcomitrella patens. BMC Evolutionary Biology*, *7*(1), 130. doi:10.1186/1471-2148-7-130 PMID:17683536

Reski, R., Parsons, J., & Decker, E. L. (2015). Moss-made pharmaceuticals: From bench to bedside. *Plant Biotechnology Journal*, *13*(8), 1191–1198. doi:10.1111/pbi.12401 PMID:26011014

Reutter, K., & Reski, R. (1996). Production of a heterologous protein in bioreactor cultures of fully differentiated moss plants. *Plant Tissue Culture & Biotechnology*, *2*, 142–147.

Rho, J., Mead, J. R., Wright, W. S., Brenner, D. E., Stave, J. W., Gildersleeve, J. C., & Lampe, P. D. (2014). Discovery of sialyl Lewis A and Lewis X modified protein cancer biomarkers using high density antibody arrays. *Journal of Proteomics*, *96*, 291–299. doi:10.1016/j.jprot.2013.10.030 PMID:24185138

Rho, S.-S., Park, S.-J., Hwang, S.-L., Lee, M.-H., Kim, C. D., Lee, I.-H., ... Rang, M. (2005). The hair growth promoting effect of Asiasari radix extract and its molecular regulation. *Journal of Dermatological Science*, *38*(2), 89–97. doi:10.1016/j.jdermsci.2004.12.025 PMID:15862941

Ribeiro-Varandas, E., Ressureição, F., Viegas, W., & Delgado, M. (2014). Cytotoxicity of *Eupatorium cannabinum* L. extracts against colon cancer cells and interactions with bisphenol A and doxorubicin. *BMC Complementary and Alternative Medicine*, *14*(1), 264. doi:10.1186/1472-6882-14-264 PMID:25056133

Rice, L. B. (2010). Progress and challenges in implementing the research on ESKAPE pathogens. *Infection Control and Hospital Epidemiology*, *31*(1), S7–S10. doi:10.1086/655995 PMID:20929376

Rico, C. M., Majumdar, S., Duarte, G. M., Peralta, V. J. R., & Gardea, T. J. L. (2011). Interaction of nanoparticles with edible plants and their possible implications in the food chain. *Journal of Agricultural and Food Chemistry*, *59*(8), 3485–3498. doi:10.1021/jf104517j PMID:21405020

Rochanakij, S. U. D. A. R. A. T. A. N. A., Thebtaranonth, Y. O. D. H. A. T. H. I., Yenjai, C., & Yuthavong, Y. (1985). Nimbolide, a constituent of *Azadirachta indica*, inhibits Plasmodium falciparum in culture. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *16*(1), 66–72. PMID:3895455

Rodriguez, B. M., Cruz, N. I., & Suarez, A. (1988). Comparative evaluation of *Aloe vera* in management of burn wounds in guinea pigs. *Plastic and Reconstructive Surgery*, *81*(3), 386–389. doi:10.1097/00006534-198803000-00012 PMID:3340673

Roh, S.-S., Kim, C. D., Lee, M.-H., Hwang, S.-L., Rang, M.-J., & Yoon, Y.-K. (2002). The hair growth promoting effect of Sophora flavescens extract and its molecular regulation. *Journal of Dermatological Science*, *30*(1), 43–49. doi:10.1016/S0923-1811(02)00060-9 PMID:12354419

Roopashree, T. S., Dang, R., Rani, R. H. S., & Narendra, C. (2008). Antibacterial activity of antipsoriatic herbs: *Cassia tora, Momordica charantia* and *Calendula officinalis. International Journal of Applied Research in Natural Products*, *1*, 20–28.

Roper, C., Pearce, R., Nair, S., Sharp, B., Nosten, F., & Anderson, T. (2004). Intercontinental spread of pyrimethamine-resistant malaria. *Science*, *305*(5687), 1124. doi:10.1126cience.1098876 PMID:15326348

Rosales-Mendoza, S., Orellana-Escobedo, L., Romero-Maldonado, A., Decker, E. L., & Reski, R. (2014). The potential of *Physcomitrella patens* as a platform for the production of plant-based vaccines. Expert Rev. *Expert Review of Vaccines*, *13*(2), 203–212. doi:10.1586/14760584.2014.872987 PMID:24405402

Roy, A., & Saraf, S. (2006). Overview of significant bioactive triterpenes distributed in plants kingdom. *Biological & Pharmaceutical Bulletin*, *29*(2), 191–201. doi:10.1248/bpb.29.191 PMID:16462017

Roychoudhury, N., & Mishra, R. (2016). *Ginko biloba* Linn.: A promising species of potential importance. *Van Sangyan*, *3*, 35–37.

Roy, N. K., Deka, A., Bordoloi, D., Mishra, S., Kumar, A. P., Sethi, G., & Kunnumakkara, A. B. (2016). The potential role of boswellic acids in cancer prevention and treatment. *Cancer Letters*, *377*(1), 74–86. doi:10.1016/j.canlet.2016.04.017 PMID:27091399

Roy, R. K., Thakur, M., & Dixit, V. K. (2007). Development and evaluation of polyherbal formulation for hair growth–promoting activity. *Journal of Cosmetic Dermatology*, *6*(2), 108–112. doi:10.1111/j.1473-2165.2007.00305.x PMID:17524127

Roy, R. K., Thakur, M., & Dixit, V. K. (2007). Effect of citrullus colocynthis. On hair growth in albino rats. *Pharmaceutical Biology*, *45*(10), 739–744. doi:10.1080/13880200701585709

Roy, R. K., Thakur, M., & Dixit, V. K. (2008). Hair growth promoting activity of *Eclipta alba* in male albino rats. *Archives of Dermatological Research*, *300*(7), 357–364. doi:10.100700403-008-0860-3 PMID:18478241

Ruan, J., Liu, Z., Qiu, F., Shi, H., & Wang, M. (2019). Simultaneous quantification of five sesquiterpene components after ultrasound extraction in *Artemisia annua* L. by an accurate and rapid UPLC-PDA assay. *Molecules*, *24*(8).

Ruan, Z. P., Zhang, L. L., & Lin, Y. M. (2008). Evaluation of the antioxidant activity of S*yzygium cumini* leaves. *Molecules (Basel, Switzerland)*, *13*(10), 2545–2556. doi:10.3390/molecules13102545 PMID:18927517

Rucker, G., Heiden, K., & Schenkel, E. (2001). Antitumor-active lactones from *Kaunia rufescens* and *Eupatorium cannabinum. Journal of the Indian Institute of Science*, *81*, 333–334.

Russo, A., & Borrelli, F. (2005). Bacopa monniera, a reputed nootropic plant: An overview. *Phytomedicine*, *12*(4), 305–317. doi:10.1016/j.phymed.2003.12.008 PMID:15898709

Rutto, L. K., Xu, Y., Ramirez, E., & Brandt, M. (2013). Mineral properties and dietary value of raw and processed stinging nettle (*Urtica dioica* L.). *International Journal of Food Sciences*. PMID:26904610

Ryu, D. D. Y., & Nam, D. H. (2000). Recent progress in biomolecular engineering. *Biotechnology Progress*, *16*(1), 2–16. doi:10.1021/bp088059d PMID:10662483

Ryu, J. K., Kim, H. S., & Nam, D. H. (2012). Current status and perspectives of biopharmaceutical drugs. *Biotechnology and Bioprocess Engineering; BBE*, *17*(5), 900–911. doi:10.100712257-012-0095-1

Saad, M., Iwagawa, T., Doe, M., & Nakatani, M. (2003). Swietenialides, novel ring D opened phragmalin limonoid orthoesters from *Swietenia mahogani* Jacq. *Tetrahedron*, *59*(40), 8027–8033. doi:10.1016/j.tet.2003.08.033

Sabovljević, A., Soković, M., Glamočlija, J., Ćirić, A., Vujičić, M., Pejin, B., & Sabovljević, M. (2011). Bio-activities of extracts from some axenically farmed and naturally grown bryophytes. *Journal of Medicinal Plants Research*, *5*(4), 565–571.

Sabu, M. C., & Kuttan, R. (2009). Antidiabetic and antioxidant activity of *Terminalia belerica*. Roxb. *Indian Journal of Experimental Biology*, *47*(4), 270–275. PMID:19382723

Safayhi, H., Mack, T., Sabieraj, J., Anazodo, M. I., Subramanian, L. R., & Ammon, H. P. (1992). Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. *Journal of Pharmacology and Experimental Therapeutics, 261*(3), 1143-1146.

Saha, K., Lajis, N. H., Israf, D. A., Hamzah, A. S., Khozirah, S., Khamis, S., & Syahida, A. (2004). Evaluation of antioxidant and nitric oxide inhibitory activities of selected Malaysian medicinal plants. *Journal of Ethnopharmacology*, *92*(2-3), 263–267. doi:10.1016/j.jep.2004.03.007 PMID:15138010

Saha, S., & Goswami, G. (2010). Study of antiulcer activity of *Ficus religiosa* L. on experimentally induced gastric ulcers in rats. *Asian Pacific Journal of Tropical Medicine*, *3*(10), 791–793. doi:10.1016/S1995-7645(10)60189-7

Saidi, Y., Finka, A., Chakhporanian, M., Zryd, J.-P., Schaefer, D. G., & Goloubinoff, P. (2005). Controlled expression of recombinant proteins in *Physcomitrella patens* by a conditional heat-shock promoter: A tool for plant research and biotechnology. *Plant Molecular Biology*, *59*(5), 697–711. doi:10.100711103-005-0889-z PMID:16270224

Said, O., Khalil, K., Fulder, S., & Azaizeh, H. (2002). Ethnobotanical survey of medicinal herbs of the Middle Eastern region. *Journal of Ethnopharmacology*, *83*, 251–265. doi:10.1016/S0378-8741(02)00253-2 PMID:12426094

Saifuddin, N., Wong, C. W., & Yasumira, A. A. N. (2009). Rapid biosynthesis of silver nanoparticles using culture supernatant of bacteria with microwave irradiation. *E-Journal of Chemistry*, *6*(1), 61–70. doi:10.1155/2009/734264

Saiin, C., Rattanajak, R., Kamchonwongpaisan, S., Ingkaninan, K., Sukontason, K., Baramee, A., & Sirithunyalug, B. (2003). Isolation and *in vitro* antimalarial activity of hexane extract from Thai Picrasma javanica B1 stembark. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *34*(2), 51–55. PMID:19230571

Saiin, C., Sirithunyalug, B., Rattanajak, R., Kamchonwongpaisan, S., Baramee, A., Sukontason, K., & Ingkaninan, K. (2016). Isolation and in vitro antimalarial activity of chloroform extract from Thai Picrasma javanica Bl stembark. *Advancement in Medicinal Plant Research*, *4*(3), 94–98.

Saini, R. K., Nile, S. H., & Park, S. W. (2015). *Carotenoids from fruits and vegetables: Chemistry, analysis, occurrence, bioavailability and biological activities. In Food Research International*. Elsevier.

Sakagami, H., Kushida, T., Makino, T., Hatano, T., Shirataki, Y., & Matsuta, T. (2012). Functional analysis of natural polyphenols and saponins as alternative medicines. Academic Press. doi:10.5772/30449

Sakihama, Y., Cohen, M. F., Grace, S. C., & Yamasaki, H. (2002). Plant phenolic antioxidant and prooxidant activities: Phenolics-induced oxidative damage mediated by metals in plants. *Toxicology*, *177*(1), 67–80. doi:10.1016/S0300-483X(02)00196-8 PMID:12126796

Saleem, T. M., Ramadurg, B., Kumar, R. P., Priyanka, N., Madhuri, M., Sravanti, U., & Sarala, K. (2012). Antiulcerogenic effect of aqueous extract of *Annona squamosa* Linn. *International Journal of Research in Phytochemistry & Pharmacology*, *2*(3), 157–159.

Saleh, M. M., Qader, S. W., & Thaker, A. A. (2016). Gastroprotective activity of *Eruca sativa* leaf extract on ethanol-induced gastric mucosal injury in *Rattus norvegicus*. *Jordan Journal of Biological Sciences*, *9*(1), 47–52. doi:10.12816/0027027

Sánchez-Mendoza, M. E., Reyes-Trejo, B., Sánchez-Gómez, P., Rodríguez-Silverio, J., Castillo-Henkel, C., Cervantes-Cuevas, H., & Arrieta, J. (2010). Bioassay-guided isolation of an anti-ulcer chromene from *Eupatorium aschenbornianum*: Role of nitric oxide, prostaglandins and sulfhydryls. *Fitoterapia*, *81*(1), 66–71. doi:10.1016/j.fitote.2009.07.009 PMID:19651191

Sangmai, T. K., Meitei, U. D., Sanjenbam, R., & Khumbongmayum, S. (2010). Diuretic property of aqueous extract of leaves of *Mimosa pudica* Linn on experimental albino rats. *Journal of Natural Products*, *3*, 173–178.

Sanna, V., Pala, N., Dessì, G., Manconi, P., Mariani, A., Dedola, S., & Sechi, M. (2014). Single-step green synthesis and characterization of gold-conjugated polyphenol nanoparticles with antioxidant and biological activities. *International Journal of Nanomedicine*, *9*, 4935–4951. PMID:25364251

Sanphui, P., Goud, N. R., Khandavilli, U. R., Bhanoth, S., & Nangia, A. (2011). New polymorphs of curcumin. *Chemical Communications*, *47*(17), 5013–5015. doi:10.1039/c1cc10204d PMID:21431190

Santram, L., & Singhai, A. K. (2011). Preliminary pharmacological evaluation of *Martynia annua* Linn leaves for wound healing. *Asian Pacific Journal of Tropical Biomedicine*, *1*(6), 421–427. doi:10.1016/S2221-1691(11)60093-2 PMID:23569806

Sareer, O., Ahmad, S., & Umar, S. (2014). *Andrographis paniculata*: A critical appraisal of extraction, isolation and quantification of andrographolide and other active constituents. *Natural Product Research*, *28*(23), 2081–2101. doi:10.1080/14786419.2014.924004 PMID:24912126

Sarkar, A., Sarkar, D., & Poddar, K. (2019). Plant metabolites as new leads to drug discovery: approaches and challenges. Medicinal Plants: Chemistry, Pharmacology and Therapeutic Applications, 61.

Sarkar, M., Das, G., Pathak, S. K., Maitra, S., & Samanta, A. (2013). Evaluation of in vivo wound healing and in vitro antibacterial activities of the different extract of *Leucas indica* Linn. *International Journal of Pharmacy and Pharmaceutical Sciences*, *5*(3), 333–340.

Sarmiento, W. C., Maramba, C. C., & Gonzales, M. L. M. (2011). An *in-vitro* study on the antibacterial effect of neem (*Azadirachta indica*) leaf extract on methicillin-sensitive and Methicillin-resistant *Staphylococcus aureus. PIDSP J.*, *12*, 40–45.

Sathish, K. K., Amutha, R., Palaniappan, A., & Sheela, B. (2011). Synthesis of gold nanoparticles: An ecofriendly approach using *Hansenula anomala. ASC Applied Materials & Interfaces*, *3*(5), 1418–1425. doi:10.1021/am200443j PMID:21517037

Sathyapalan, T., Kilpatrick, E. S., Rigby, A. S., Thatcher, N. J., & Atkin, S. L. (2014, June). The effect of soy phytoestrogens on cardiovascular risk markers in men with type 2 diabetes and subclinical hypogonadism-a randomised double blind parallel study. Endocrine Reviews, 35(3).

Sato, Y., Oketani, H., Singyouchi, K., Ohtsubo, T., Kihara, M., Shibata, H., & Higuti, T. (1997). Extraction and purification of effective antimicrobial constituents of *Terminalia chebula* Rets. against methicillin-resistant *Staphylococcus aureus*. *Biological & Pharmaceutical Bulletin*, *20*(4), 401–404. doi:10.1248/bpb.20.401 PMID:9145218

Saxena, D., & Harinder. (2004). Uses of bryophytes. *Resonance*, *9*(6), 56–65. doi:10.1007/BF02839221

Schillberg, S., Twyman, R. M., & Fischer, R. (2005). Opportunities for recombinant antigen and antibody expression in transgenicn plants-technology assessment. *Vaccine*, *23*(15), 1764–1769. doi:10.1016/j.vaccine.2004.11.002 PMID:15734038

Schmidt, A. (2013). *Composition and uses for influencing hair growth*. Google Patents.

Schmidt, F. R. (2004). Recombinant expression systems in the pharmaceutical industry. *Applied Microbiology and Biotechnology*, *65*(4), 363–372. doi:10.100700253-004-1656-9 PMID:15480623

Schmidtko, J., Peine, S., El-Housseini, Y., Pascual, M., & Meier, P. (2013). Treatment of atypical hemolytic uremic syndrome and thrombotic microangiopathies: A focus on Eculizumab. *American Journal of Kidney Diseases*, *61*(12), 289–299. doi:10.1053/j.ajkd.2012.07.028 PMID:23141475

Schofield, P., Mbugua, D. M., & Pell, A. N. (2001). Analysis of condensed tannins: A review. In *Animal Feed Science and Technology*. Elsevier.

Schuster, M., Jost, W., Mudde, G. C., Wiederkum, S., Schwager, C., Janzek, E., ... Gorr, G. (2007). *In vivo* glycoengineered antibody with improved lytic potential produced by an innovative non-mammalian expression system. *Biotechnology Journal: Healthcare Nutrition Technology*, *2*(6), 700–708. doi:10.1002/biot.200600255 PMID:17427997

Scotece, M., Gomez, R., Conde, J., Lopez, V., Gomez-Reino, J. J., Lago, F., ... Gualillo, O. (2013). Oleocanthal inhibits proliferation and MIP-1α expression in human multiple myeloma cells. *Current Medicinal Chemistry*, *20*(19), 2467–2475. doi:10.2174/0929867311320190006 PMID:23521677

Selvakannan, P. R., Mandal, S., Pasricha, R., Adyanthaya, S. D., & Sastry, M. (2002). One-step synthesis of hydrophobized gold nanoparticles of controllable size by the reduction of aqueous chloroaurate ions by hexadecylaniline at the liquid-liquid interface. *Chemical Communications*, *13*(13), 1334–1335. doi:10.1039/b203438g

Semalty, M., Semalty, A., Joshi, G. P., & Rawat, M. S. M. (2010). *In vivo* hair growth activity of herbal formulations. *International Journal of Pharmacology*, *6*, 53–57. doi:10.3923/ijp.2010.53.57

Senatore, F., De Fusco, R., & Napplitano, F. (2001). *Eupatorium cannabinum* L. ssp. *cannabinum* (Asteraceae) essential oils. Chemical composition and antibacterial activity. *The Journal of Essential Oil Research*, *13*(6), 463–466. doi:10.1080/10412905.2001.9699730

Sengupta, M., Sharma, G. D., & Chakraborty, B. (2011). Effect of aqueous extract of *Tinospora cordifolia* on functions of peritoneal macrophages isolated from CCl4 intoxicated male albino mice. *BMC Complementary and Alternative Medicine*, *11*(1), 102. doi:10.1186/1472-6882-11-102 PMID:22035196

Sen, S., & Chakroborty, R. (2015). Towards the integration and advancement of herbal medicines: A focus on traditional Indian medicine. *Botanics: Targets and Therapy*, *5*, 33–44. doi:10.2147/BTAT.S66308

Sethi, S., Nester, C. M., & Smith, R. J. H. (2012). Membranoproliferative glomerulonephritis and C3 glomerulopathy: Resolving the confusion. *Kidney International*, *81*(5), 434–441. doi:10.1038/ki.2011.399 PMID:22157657

Shah, C. S., & Qadri, J. S. (1990). *Text book of pharmacognosy (Shah, BS), prakashan*. Academic Press.

Shahidi, F. (2015). *Antioxidants: Principles and Applications. Handbook of Antioxidants for Food Preservation*. Elsevier Ltd.

Shahidi, F., Janitha, P. K., & Wanasundara, P. D. (1992). Phenolic antioxidants. *Critical Reviews in Food Science and Nutrition*, *32*(1), 67–103. doi:10.1080/10408399209527581 PMID:1290586

Shahid, M., Rhaim, T., & Shahzad, A., Tajuddin, Latif, A., Fatma, T., … Mustafa, S. (2009). Ethnobotanical studies on *Berberis aristata* D.C. root extract. *African Journal of Biotechnology*, *8*(40), 556–563.

Shaikh, M. F., Sancheti, J., & Sathaye, S. (2012). Phytochemical and pharmacological investigations of *Eclipta alba* (Linn.) Hassak leaves for antiepileptic activity. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(4), 319–323.

Shaikh, R. M., Baqir, M. F., Naqvi, S., & Shaikh, D. (1994). Partial purification and antibacterial studies of extracts from *Eugenia jambolana* Linn and *Vincarosea* Linn. *Pakistan Journal of Scientific and Industrial Research*, *37*, 279–281.

Shamaila, S., Zafar, N., Riaz, S., Sharif, R., Nazir, J., & Naseem, S. (2016). Gold nanoparticles: An efficient antimicrobial agent against enteric bacterial human pathogen. *Nanomaterials (Basel, Switzerland)*, *6*(4), 71–80. doi:10.3390/nano6040071 PMID:28335198

Shamkuwar, P. B., Pawar, D. P., & Chauhan, S. S. (2012). Antidiarrhoeal activity of seeds of *Syzygium cumini* L. *Journal of Pharmacy Research*, *5*(12).

Shanbhag, T. V., Sharma, C., Adiga, S., Bairy, K. L., Shenoy, S., & Shenoy, G. (2006). Wound healing activity of alcoholic extract of *Kaempferia galanga* in Wistar rats. *Indian Journal of Physiology and Pharmacology*, *50*(4), 384–390. PMID:17402268

Shao, Y., Ho, C. T., Chin, C. K., Badmaev, V., Ma, W., & Huang, M. T. (1998). Inhibitory activity of boswellic acids from *Boswellia serrata* against human leukemia HL-60 cells in culture. *Planta Medica*, *64*(04), 328–331. doi:10.1055-2006-957444 PMID:9619114

Sharififar, F., Dehghn-Nudeh, G., & Mirtajaldini, M. (2009). Major flavonoids with antioxidant activity from *Teucrium polium* L. *Food Chemistry*, *112*(4), 885–888. doi:10.1016/j.foodchem.2008.06.064

Sharma, S.B., Nasir, A., Prabhu, K.M., Murthy, P.S., & Dev, G. (2003). Hypoglycaemic and hypolipidemic effect of ethanolic extract of seeds of *Eugenia jambolana* in alloxan-induced diabetic rabbits. *Journal of Ethnopharmacology, 85*(2), 201-206.

Sharma, A. K., Agarwal, V., Kumar, R., Kaushik, K., Bhardwaj, P. H., & Chaurasia, H. (2010). Development and evaluation of herbal formulation for hair growth. *International Journal of Current Trends in Science and Technology*, *1*, 147–151.

Sharma, B. C. (2013). In vitro antibacterial activity of certain folk medicinal plants from Darjeeling Himalayas used to treat microbial infections. *Journal of Pharmacognosy and Phytochemistry*, *2*(4), 1–4.

Sharma, G., Rao, S., Bansal, A., Dang, S., Gupta, S., & Gabrani, R. (2014). *Pseudomonas aeruginosa* biofilm: Potential therapeutic targets. *Biologicals*, *42*(1), 1–7. doi:10.1016/j.biologicals.2013.11.001 PMID:24309094

Sharma, K., Bairwa, R., Chauhan, N., Shrivastava, B., & Saini, N. K. (2011). Beberis aristata [review]. *International Journal of Research and Analytical Review*, *2*(2), 383–388.

Sharma, P. V. (1999). *Dravyaguna Vijnana* (Vol. 2). Varanasi: Chaukhambha Bharti Academy.

Sharma, R. A., McLelland, H. R., Hill, K. A., Ireson, C. R., Euden, S. A., Manson, M. M., & Steward, P. (2001). Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clinical Cancer Research*, *7*(7), 1894–1900.

Sharma, U., Bala, M., Kumar, N., Singh, B., Munshi, R. K., & Bhalerao, S. (2012). Immuno modulatory active compounds from *Tinospora cordifolia*. *Journal of Ethnopharmacology*, *141*(3), 918–926. doi:10.1016/j.jep.2012.03.027 PMID:22472109

Sharma, V., & Pandey, D. (2010). Beneficial effects of *Tinosporacordifolia*on blood profiles in male mice exposed to lead. *Toxicology International*, *17*(1), 8. doi:10.4103/0971-6580.68341 PMID:21042466

Shedbalkar, U., Singh, R., Wadhwani, S., Gaidhani, S., & Chopade, B. A. (2014). Microbial synthesis of gold nanoparticles: Current status and future prospects. *Advances in Colloid and Interface Science*, *209*, 40–48. doi:10.1016/j.cis.2013.12.011 PMID:24456802

Shidfar, F., Froghifar, N., Vafa, M., Rajab, A., Hosseini, S., Shidfar, S., & Gohari, M. (2011). The effects of tomato consumption on serum glucose, apolipoprotein B, apolipoprotein A-I, homocysteine and blood pressure in type-2 diabetic patients. *International Journal of Food Sciences and Nutrition*, *62*(3), 289–294. doi:10.3109/09637486.2010.529072 PMID:21138408

Shi, J.-S., Yu, J.-X., Chen, X.-P., & Xu, R.-X. (2003). Pharmacological actions of *Uncaria* alkaloids, rhynchophylline and isorhynchophylline. *Acta Pharmacologica Sinica*, *24*(2), 97–101. PMID:12546715

Shinde, V., Borkar, A., & Badwaik, R. (2014). Evaluation and comparative study of hypoglycemic activity of aloe Barbadensis Miller with oral hypoglycemic drugs (glibenclamide and metformin) in rats. *International Journal of Medical and Pharmaceutical Sciences*, *4*(6), 31–36.

Shin, S. K., Ha, T. Y., McGregor, R. A., & Choi, M. S. (2011). Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. *Molecular Nutrition & Food Research*, *55*(12), 1829–1840. doi:10.1002/mnfr.201100440 PMID:22058071

Shi, Q. W., Li, L. G., Huo, C. H., Zhang, M. L., & Wang, Y. F. (2010). Study on natural medicinal chemistry and new drug development. *Chinese Traditional and Herbal Drugs*, *41*, 1583–1589.

Shirwaikar, A., Jahagirdar, S., & Udupa, A. L. (2003). Wound healing activity of *Desmodium triquetrum* leaves. *Indian Journal of Pharmaceutical Sciences*, *65*(5), 461–464.

Shivananjappa, M. M., & Muralidhara. (2012). Abrogation of maternal and fetal oxidative stress in the streptozotocin-induced diabetic rat by dietary supplements of *Tinospora cordifolia*. *Nutrition (Burbank, Los Angeles County, Calif.)*, *28*(5), 581–587. doi:10.1016/j.nut.2011.09.015 PMID:22189193

Shori, A. B. (2015). Screening of antidiabetic and antioxidant activities of medicinal plants. *Journal of Integrative Medicine*, *13*(5), 297–305. doi:10.1016/S2095-4964(15)60193-5 PMID:26343100

Shree Devi, M. S. (2011). Acute toxicity and diuretic activity of *Mangifera indica* Linn bark extracts. *International Journal of Pharmacology and Biosciences*, *2*, 141–146.

Shrestha, S., Ehlers, S. J., Lee, J. Y., Fernandez, M. L., & Koo, S. I. (2009). Dietary green tea extract lowers plasma and hepatic triglycerides and decreases the expression of sterol regulatory element-binding protein-1c mRNA and its responsive genes in fructose-fed, ovariectomized rats. *The Journal of Nutrition*, *139*(4), 640–645. doi:10.3945/jn.108.103341 PMID:19193814

Shrivastava, S., Bera, T., Roy, A., Singh, G., Ramachandrarao, P., & Dash, D. (2007). Characterization of enhanced antibacterial effects of novel silver nanoparticles. *Nanotechnology*, *18*(22), 103–112. doi:10.1088/0957-4484/18/22/225103

Siddique, A. B., Ayoub, N. M., Tajmim, A., Meyer, S. A., Hill, R. A., & El Sayed, K. A. (2019). (-)-Oleocanthal prevents breast cancer loco regional recurrence after primary tumour surgical excision and neoadjuvant targeted therapy in orthotropic nude mouse models. *Cancers (Basel)*, *11*(5), 637. doi:10.3390/cancers11050637 PMID:31072015

Siddiqui, M. Z. (2011). *Boswellia serrata*, a potential antiinflammatory agent: An overview. *Indian Journal of Pharmaceutical Sciences*, *73*(3), 255. PMID:22457547

Siebertz, R., Proksch, P., Wray, V., & Witte, L. (1989). Accumulation and biosynthesis of benzofurans in root cultures of *Eupatorium cannabinum*. *Phytochemistry*, *28*(3), 789–793. doi:10.1016/0031-9422(89)80116-5

Singaravelu, G., Arockiyamari, J., Ganesh, K. V., & Govindaraju, K. (2007). A novel extracellular biosynthesis of monodisperse gold nanoparticles using marine algae, *Sargassum wightii* Greville. *Colloids and Surfaces. B, Biointerfaces*, *57*(1), 97–101. doi:10.1016/j.colsurfb.2007.01.010 PMID:17350236

Singh, M., Saxena, A. & Neeraj, P.K. (2015). Study of the larvicidal effect of *Eupatorium cannabinum* Linn (Family Asteraceae) leaf extract on *Callosobruchus chinensis* Linn (Family Bruchidae). *International Interdisciplinary Research Journal,* S42-50.

Singh, R. K. (2014). *Therapeutic Uses of Curcumin Spice*. Academic Press.

Singh, G. B., & Atal, C. K. (1986). Pharmacology of an extract of salaiguggal ex-*Boswellia serrata*, a new non-steroidal anti-inflammatory agent. *Agents and Actions*, *18*(3-4), 407–412. doi:10.1007/BF01965005 PMID:3751752

Singh, H. B., Prasad, P., & Rai, L. K. (2002). Folk medicinal plants in the Sikkim Himalayas of India. *Asian Folklore Studies*, *61*(2), 295–310. doi:10.2307/1178975

Singh, K., Panghal, M., Kadyan, S., Chaudhary, U., & Yadav, J. P. (2014). Antibacterial activity of synthesized silver nanoparticles from *Tinospora cordifolia* against multi drug resistant strains of *Pseudomonas aeruginosa* isolated from burn patients. *Journal of Nanomedicine & Nanotechnology*, *5*(2), 1–6. doi:10.4172/2157-7439.1000192

Singh, N., Dixit, V., Irchhaiya, R., & Alok, S. (2016). Wound healing activity of *Mimusops elengi* Linn. *International Journal of Pharmaceutical Sciences and Research*, *7*(1), 349–352.

Singh, N., Singh, S. M., & Shrivastava, P. (2005). Immunomodulatory and antitumor actions of medicinal plant *Tinospora cordifolia* are mediated through activation of tumor-associated macrophages. *Immunopharmacology and Immunotoxicology*, *26*(1), 145–162. doi:10.1081/IPH-120029952 PMID:15106739

Singh, P. K., Roy, S., & Dey, S. (2003). Antimicrobial activity of *Andrographis paniculata. Fitoterapia*, *74*(7-8), 692–694. doi:10.1016/S0367-326X(03)00159-X PMID:14630176

Singh, R. (2015). Medicinal plants: A review. *Journal of Plant Sciences*, *3*, 50–55.

Singh, R. P., Banerjee, S., Kumar, P. V., Raveesha, K. A., & Rao, A. R. (2006). *Tinospora cordifolia* induces enzymes of carcinogen/drug metabolism and antioxidant system and inhibits lipid peroxidation in mice. *Phytochemistry*, *13*(1-2), 74–84. PMID:16360936

Singh, R., Singh, S., Kumar, S., & Arora, S. (2007). Evaluation of antioxidant potential of ethyl acetate extract/fractions of *Acacia auriculiformis* A. Cunn. *Food and Chemical Toxicology*, *45*(7), 1216–1223. doi:10.1016/j.fct.2007.01.002 PMID:17336438

Singh, S. S., Pandey, S. C., Srivastava, S., Gupta, V. S., Patro, B., & Ghosh, A. C. (2003). Chemistry and medicinal properties of *Tinospora cordifolia* (Guduchi). *Indian Journal of Pharmacology*, *35*(2), 83–91.

Singh, S. S., Pandey, S. C., Srivastava, S., Gupta, V. S., Patro, B., & Ghosh, A. C. (2003). Chemistry and medicinal properties of *Tinospora cordifolia. Indian Journal of Pharmacology*, *35*, 83–91.

Singh, S., Khajuria, A., Taneja, S. C., Johri, R. K., Singh, J., & Qazi, G. N. (2008). Boswellic acids: A leukotriene inhibitor also effective through topical application in inflammatory disorders. *Phytomedicine*, *15*(6-7), 400–407. doi:10.1016/j.phymed.2007.11.019 PMID:18222672

Singh, S., & Majumdar, D. K. (1999). Evaluation of the gastric antiulcer activity of fixed oil of *Ocimum sanctum* (Holy Basil). *Journal of Ethnopharmacology*, *65*(1), 13–19. doi:10.1016/S0378-8741(98)00142-1 PMID:10350365

Singh, S., Taneja, M., & Majumdar, D. K. (2007). Biological activities of *Ocimum sanctum* L. fixed oil- An overview. *Indian Journal of Experimental Biology*, *45*, 403–412. PMID:17569280

Singh, T. Th., Devi, A. R., Sharma, H. R., & Sharma, M. H. (2016). Plants used in the treatment of stomach problems by the scheduled caste community of Andro village in Imphal East District, Manipur, India. *International Journal of Current Research and Academic Review*, *4*(1), 23–38. doi:10.20546/ijcrar.2016.401.003

Sinha, S. C. & Mass. (1996). *Medicinal Plants of Manipur*. In Manipur Cultural Integration Conference, Imphal, Manipur, India.

Sinou, V., Pelleau, S., Huong, V. N., Huong, N. T., Bertaux, L., Desbordes, M., & Parzy, D. (2011). Polymorphism of Plasmodium falciparum Na+/H+ exchanger is indicative of a low in vitro quinine susceptibility in isolates from Viet Nam. *Malaria Journal*, *10*(1), 164. doi:10.1186/1475-2875-10-164 PMID:21669011

Sivagamy, M., Jeganathan, M. R., Manavalan, R., & Senthamarai, R. (2012). Wound healing activity of *Indigofera enneaphylla* Linn. *Int J Adv Pharm Chem Biol*, *1*(2), 211–214.

Sivasubramanian, A., Gadepalli, N. K. K., Rathnasamy, R., & Campos, A. M. (2013). A new antifeedant clerodane diterpenoid from *Tinospora cordifolia. Natural Product Research*, *27*(16), 1431–1436. doi:10.1080/14786419.2012.722088 PMID:22946632

Škrovánková, S., Mišurcová, L., & Machů, L. (2012). Antioxidant activity and protecting health effects of common medicinal plants. *Advances in Food and Nutrition Research*, *67*, 75–139. doi:10.1016/B978-0-12-394598-3.00003-4 PMID:23034115

Smitha, S. L., Philip, D., & Gopchandran, K. G. (2009). Green synthesis of gold nanoparticles using Cinnamomum zeylanicum leaf broth. *Spectrochimica Acta. Part A: Molecular and Biomolecular Spectroscopy*, *74*(3), 735–739. doi:10.1016/j.saa.2009.08.007 PMID:19744880

Smithson, J., Kellick, K. A., & Mergenhagen, K. (2017). Nutritional modulators of pain in the aging population. In *Nutritional Modulators of Pain in the Aging Population* (pp. 191–198). Academic Press. doi:10.1016/B978-0-12-805186-3.00016-3

Sokmen, M., Angelova, M., Krumova, E., Pashova, S., Ivancheva, S., Sokmen, A., & Serkedjieva, J. (2005). *In vitro* antioxidant activity of polyphenol extracts with antiviral properties from *Geranium sanguineum* L. *Life Sciences*, *76*(25), 2981–2993. doi:10.1016/j.lfs.2004.11.020 PMID:15820508

Somboonwong, J., Kankaisre, M., Tantisira, B., & Tantisira, M. H. (2012). Wound healing activities of different extracts of *Centella asiatica* in incision and burn wound models: An experimental animal study. *BMC Complementary and Alternative Medicine*, *12*(1), 103. doi:10.1186/1472-6882-12-103 PMID:22817824

Son, B. K., Kim, J. Y., & Lee, S. S. (2008). Effect of adlay, buckwheat and barley on lipid metabolism and aorta histopathology in rats fed an obesogenic diet. *Annals of Nutrition & Metabolism*, *52*(3), 181–187. doi:10.1159/000138121 PMID:18544971

Sougata, G., Sumersing, P., Mehul, A., Rohini, K., Amit, J., Sangeeta, K., & Balu, A. C. (2011). Synthesis of silver nanoparticles using *Dioscorea bulbifera* tuber extract and evaluation of its synergistic potential in combination with antimicrobial agents. *Journal of Nanomaterials*, *7*, 483–496.

Squires, R. F., Ai, J., Witt, M.-R., Kahnberg, P., Saederup, E., Sterner, O., & Nielsen, M. (1999). Honokiol and magnolol increase the number of [3 H] muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites. *Neurochemical Research*, *24*(12), 1593–1602. doi:10.1023/A:1021116502548 PMID:10591411

Srivastava, S., Jaiswal, J., Gautam, H., Sharma, S., & Rao, C. V. (2013). Anti-ulcer activity of methanol extract of *Hibiscus rosa-sinensis* leaves. *International Journal of Pharmacy and Pharmaceutical Sciences*, *5*(3), 829–830.

Srivastav, S., Singh, P., Mishra, G., Jha, K. K., & Khosa, R. L. (2011). *Achyranthes aspera* an important medicinal plant: A review. *Journal of Natural Product and Plant Resources*, *1*, 1–14.

Stanca, M.H., Nagy, A., Tosa, M. & Vlad, L. (2011). Hepatoprotective effects of orally administered melatonin and *Tinospora cordifolia* in experimental jaundice. *Chirurgia, 106*(2), 205-210.

Stanely, P., Prince, M., & Menon, V. P. (2000). Hypoglycemic and other related actions of *Tinospora cordifolia* roots in alloxan-induced diabetic rats. *Journal of Ethnopharmacology*, *70*(1), 9–15. doi:10.1016/S0378-8741(99)00136-1 PMID:10720784

Subitha, T. K., Ayyanar, M., Udayakumar, M., & Sekar, T. (2011). Ethnomedicinal plants used by Kani tribals in Pechiparai forests of Southern western Ghats, Tamil Nadu, India. *International Research Journal Plant Science*, *2*(12), 349–354.

Sudha, P., Zinjarde, S. S., Bhargava, S. Y., & Kumar, A. R. (2011). Potent α-amylase inhibitory activity of Indian Ayurvedic medicinal plants. *BMC Complementary and Alternative Medicine*, *11*(1), 5. doi:10.1186/1472-6882-11-5 PMID:21251279

Sultana, R., & Butterfield, D. A. (2010). Role of oxidative stress in the progression of Alzheimer's disease. *Journal of Alzheimer's Disease*, *19*(1), 341–353. doi:10.3233/JAD-2010-1222 PMID:20061649

Sumitra, M., Manikandan, P., & Suguna, L. (2005). Efficacy of *Butea monosperma* on dermal wound healing in rats. *The International Journal of Biochemistry & Cell Biology*, *37*(3), 566–573. doi:10.1016/j.biocel.2004.08.003 PMID:15618014

Sun, J., Deng, Z., & Yan, A. (2014). Bacterial multidrug efflux pumps: Mechanisms, physiology and pharmacological exploitations. *Biochemical and Biophysical Research Communications*, *2*(453), 254–267. doi:10.1016/j.bbrc.2014.05.090 PMID:24878531

Sun, Y., & Xia, Y. (2002). Shape-controlled synthesis of gold and silver nanoparticles. *Science*, *298*(5601), 2176–2179. doi:10.1126cience.1077229 PMID:12481134

Surveswaran, S., Cai, Y. Z., Corke, H., & Sun, M. (2007). Systematic evaluation of natural phenolic antioxidants from 133 Indian medicinal plants. *Food Chemistry*, *102*(3), 938–953. doi:10.1016/j.foodchem.2006.06.033

Swamy, H. K., Krishna, V., Shankarmurthy, K., Rahiman, B. A., Mankani, K. L., Mahadevan, K. M., ... Naika, H. R. (2007). Wound healing activity of embelin isolated from the ethanol extract of leaves of *Embelia ribes* Burm. *Journal of Ethnopharmacology*, *109*(3), 529–534. doi:10.1016/j.jep.2006.09.003 PMID:17034970

Syafruddin, D., Siregar, J. E., & Marzuki, S. (1999). Mutations in the cytochrome b gene of *Plasmodium berghei* conferring resistance to atovaquone. *Molecular and Biochemical Parasitology*, *104*(2), 185–194. doi:10.1016/S0166-6851(99)00148-6 PMID:10593174

Syed, B., Prasad, N. M. N., & Satish, S. (2016). Endogenic mediated synthesis of gold nanoparticles *bearing bactericidal activity. Journal of Microscopy and Ultrastructure*, *4*(3), 162–166. doi:10.1016/j.jmau.2016.01.004 PMID:30023223

Szalai, G., Kellos, T., Galiba, G., & Kocsy, G. (2009). Glutathione as an antioxidant and regulatory molecule in plants under abiotic stress conditions. *Journal of Plant Growth Regulation*, *28*(1), 66–80. doi:10.100700344-008-9075-2

Szent-Giörgyi, A. (1963). Lost in the twentieth century. *Annual Review of Biochemistry*, *36*(1), 1–15. doi:10.1146/annurev.bi.32.070163.000245 PMID:14140702

Szeto, S., Yow, C. M. N., & Fung, K. W. (2002). Characterization of berberine on human cancer cells in culture. *Turkish Journal of Medical Sciences*, *32*, 363–368.

Taika, B. B., Bouckandou, M., Souza, A., Bourobou, H. B., MacKenzie, L. S., & Lione, L. (2018). An overview of anti-diabetic plants used in Gabon: Pharmacology and toxicology. *Journal of Ethnopharmacology*, *216*, 203–228. doi:10.1016/j.jep.2017.12.036 PMID:29305175

Takahashi, M., Sung, B., Shen, Y., Hur, K., Link, A., Boland, C. R., & Goel, A. (2012). Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family. *Carcinogenesis*, *33*(12), 2441–2449. doi:10.1093/carcin/bgs286 PMID:22983985

Takala-Harrison, S., Clark, T. G., Jacob, C. G., Cummings, M. P., Miotto, O., Dondorp, A. M., & Bethell, D. (2013). Genetic loci associated with delayed clearance of *Plasmodium falciparum* following artemisinin treatment in Southeast Asia. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(1), 240–245. doi:10.1073/pnas.1211205110 PMID:23248304

Takasu, K., Shimogama, T., Saiin, C., Kim, H. S., Wataya, Y., & Ihara, M. (2004). π-Delocalized β- carbolinium cations as potential antimalarials. *Bioorganic & Medicinal Chemistry Letters*, *14*(7), 1689–1692. doi:10.1016/j.bmcl.2004.01.055 PMID:15026051

Taku, K., Umegaki, K., Sato, Y., Taki, Y., Endoh, K., & Watanabe, S. (2007). Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *The American Journal of Clinical Nutrition*, *85*(4), 1148–1156. doi:10.1093/ajcn/85.4.1148 PMID:17413118

Tambekar, D. H., Khante, B. S., Chandak, B. R., Titare, A. S., Boralkar, S. S., & Aghadte, S. N. (2009). Screening of antibacterial potentials of some medicinal plants from Melghat forest in India. *African Journal of Traditional, Complementary, and Alternative Medicines*, *6*, 228–232. PMID:20448847

Tamrakar, V., & Arora, C. (2019). Curcuma caesia: Present status and future prospect as herbal drug. *Progressive Agriculture*, *19*(2), 258–261. doi:10.5958/0976-4615.2019.00036.X

Tang, S. S., Apisarnthanarak, A., & Hsu, L. Y. (2014). Mechanisms of *β*-lactam antimicrobial resistance and epidemiology of major community- and healthcare-associated multidrug resistant bacteria. A*dvanced Drug Delivery Reviews,* 7*8,* 3–13. doi:10.1016/j.addr.2014.08.003 PMID:25134490

Tang, W., & Eisenbrand, G. (2013). *Chinese drugs of plant origin: chemistry, pharmacology, and use in traditional and modern medicine*. Springer Science & Business Media.

Tanwar, R. S., Sharma, S. B., Singh, U. R., & Prabhu, K. M. (2010). Attenuation of renal dysfunction by anti-hyperglycemic compound isolated from fruit pulp of *Eugenia jambolana* in streptozotocin induced diabetic rats. *Indian Journal of Biochemistry & Biophysics*, *47*, 83–89. PMID:20521620

Tao, Q. F., Xu, Y., Lam, R. Y. Y., Schneider, B., Dou, H., Leung, P. S., ... Zhao, Y. (2008). Diary heptanoids and a monoterpenoid from the rhizomes of *Zingiber officinale*: Antioxidant and cytoprotective properties. *Journal of Natural Products*, *71*(1), 12–17. doi:10.1021/np070114p PMID:18177011

Tao, Z., Shi, A., Lu, C., Song, T., Zhang, Z., & Zhao, J. (2015). Breast cancer: Epidemiology and etiology. *Cell Biochemistry and Biophysics*, *72*(2), 333–338. doi:10.100712013-014-0459-6 PMID:25543329

Taranalli, A. D., & Cheeramkuzhy, T. C. (2000). Influence of Clitoria ternatea extracts on memory and central cholinergic activity in rats. *Pharmaceutical Biology*, *38*(1), 51–56. doi:10.1076/1388-0209(200001)3811-BFT051 PMID:21214440

Teixeira, C. C., Weinert, L. S., Barbosa, D. C., Ricken, C., Esteves, J. F., & Fuchs, F. D. (2004). *Syzygium cumini* (L.) Skeels in the treatment of type 2 diabetes. *Diabetes Care*, *27*(12), 3019–3020. doi:10.2337/diacare.27.12.3019-a PMID:15562231

Tejada, S., Setzer, N., Daglia, M., Nabavi, S. F., Sureda, A., Braidy, N., ... Nabavi, S. M. (2017). Neuroprotective effects of Ellagitannins: A brief review. *Current Drug Targets*, *18*(13), 1518–1528. doi:10.2174/1389450117666161005112002 PMID:27719661

Teklehaymanot, T., & Giday, M. (2007). Ethnobotanical study of medicinal plants used by people in Zegie Peninsula, Northwestern Ethiopia. *Journal of Ethnobiology and Ethnomedicine*, *3*(1), 12. doi:10.1186/1746-4269-3-12 PMID:17355645

ter Kuile, F. O., van Eijk, A. M., & Filler, S. J. (2007). Effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy: A systematic review. *Journal of the American Medical Association*, *297*(23), 2603–2616. doi:10.1001/jama.297.23.2603 PMID:17579229

Thippeswamy, N. B., & Naidu, K. A. (2005). Antioxidant potency of cumin varieties-Cumin, black cumin and bitter cumin-On antioxidant systems. *European Food Research and Technology*, *220*(5-6), 472–476. doi:10.100700217-004-1087-y

Thomas, E. P., Colvin, M., Rosen, S. B., Zuccarini, C., & Petzer, S. (2005). *HIV prevalence study and costing analysis undertaken for the development of an HIV/AIDS workplace strategy for Buffalo City Municipality*. Medical Research Council.

Thomson, J. M., & Bonomo, R. A. (2005). The threat of antibiotic resistance in Gram-negative pathogenic bacteria: *β*-lactams in peril. C*urrent Opinion in Microbiology,* 8*(*5), 518–524. doi:10.1016/j.mib.2005.08.014 PMID:16126451

Thomson, M., Al-Qattan, K. K., Bordia, T., & Ali, M. (2006). Including garlic in the diet may help lower blood glucose, cholesterol, and triglycerides. *The Journal of Nutrition*, *136*(3), 800–802. doi:10.1093/jn/136.3.800S PMID:16484567

Thorat, R. M., Jadhav, V. M., & Kadam, V. J. (2009). Development and evaluation of polyherbal formulations for hair growth-promoting activity. *International Journal of Pharm Tech Research*, *1*(4), 1251–1254.

Tiwari, M., Dwivedi, U. N., & Kakkar, P. (2014). *Tinospora cordifolia* extract modulates COX-2, iNOS, ICAM-1, pro-inflammatory cytokines and redox status in murine model of asthma. *Journal of Ethnopharmacology*, *153*(2), 326–337. doi:10.1016/j.jep.2014.01.031 PMID:24556222

Tomotake, H., Yamamoto, N., Yanaka, N., Ohinata, H., Yamazaki, R., Kayashita, J., & Kato, N. (2006). High protein buckwheat flour suppresses hypercholesterolemia in rats and gallstone formation in mice by hypercholesterolemic diet and body fat in rats because of its low protein digestibility. *Nutrition (Burbank, Los Angeles County, Calif.)*, *22*(2), 166–173. doi:10.1016/j.nut.2005.01.012 PMID:16459229

Triantaphyllou, K., Blekas, G., & Boskou, D. (2001). Antioxidative properties of water extracts obtained from herbs of the species Lamiaceae. *International Journal of Food Sciences and Nutrition*, *52*, 313–317. doi:10.1080/09637480120057512 PMID:11474895

Tripathi, K. D. (1994). Essentials of Medical Pharmacology. Jaypee Brothers, Medical Publishers (P).

Tripathi, K. D. (2008). Essentials of Medical Pharmacology, 6thedn, India. *JP Brothers Medical Publishers*, *2008*, 613–614.

Tuhin, R. H., Begum, M. M., Rahman, M. S., Karim, R., Begum, T., Ahmed, S. U., & Begum, R. (2017). Wound healing effect of *Euphorbia hirta* Linn. (Euphorbiaceae) in alloxan induced diabetic rats. *BMC Complementary and Alternative Medicine*, *17*(1), 423. doi:10.118612906-017-1930-x PMID:28836990

Tun, K. M., Imwong, M., Lwin, K. M., Win, A. A., Hlaing, T. M., Hlaing, T., & Dhorda, M. (2015). Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: A cross-sectional survey of the K13 molecular marker. *The Lancet. Infectious Diseases*, *15*(4), 415–421. doi:10.1016/S1473-3099(15)70032-0 PMID:25704894

U.S. National Plant Germplasm System. (n.d.). *Taxon: Eupatorium cannabinum L.* https://npgsweb.arsgrin.gov/gringlobal/taxonomydetail.aspx?315553

Udayakumar, R., Kasthurirengan, S., Vasudevan, A., Mariashibu, T. S., Rayan, J. J., Choi, C. W., ... Kim, S. C. (2010). Antioxidant effect of dietary supplement *Withania somnifera* L. reduces blood glucose levels in alloxan-induced diabetic rats. *Plant Foods for Human Nutrition (Dordrecht, Netherlands)*, *65*(2), 91–98. doi:10.100711130-009-0146-8 PMID:20186490

Udem, S. C., Ezeonuegbu, U. C., & Obidike, R. I. (2011). Experimental studies on the hypolipidemic and haematological properties of aqueous leaf extract of *Cleistopholiss patens* Benth & Diets. (Annonacae) in hypercholesterolemic rats. *Annals of Medical and Health Sciences Research*, (1): 115–121. PMID:23209964

Udenze, E. C. C., Braide, V. B., Okwesilieze, C. N., & Akuodor, G. C. (2012). Pharmacological effects of *Garcinia kola* seed powder on blood sugar, lipid profile and atherogenic index of alloxan-induced diabetes in rats. *Pharmacologia*, *3*(12), 693–699. doi:10.5567/pharmacologia.2012.693.699

Ugandhar, T., Chandraiah, G., & Devi, A. (2014). Studies on ethno-medicinal plants for womenfolk's health care in ramagiri fort of mahadevapur reserve forest in karimnagar district of telangana region. *Science Research Reporter*, *4*(1), 51–56.

Ulrich, R. (1970). Organic Acids. *The Biochemistry of Fruits and Their Products*, 89-118.

Umeyama, A., Yahisa, Y., Okada, M., Okayama, E., Uda, A., Shoji, N., & Hashimoto, T. (2010). Triterpene esters from Uncaria rhynchophylla drive potent IL-12-dependent Th1 polarization. *Journal of Natural Medicines*, *64*(4), 506–509. doi:10.100711418-010-0438-1 PMID:20585989

Upadhyay, H., Kumar, A., Gupta, M. K., Sharma, A., & Rahal, A. (2013). Validation of medicinal values of traditionally used *Sonchus asper* (prickly sow thistle) leaves for the treatment of skin ailments. *Advan. Med. Plant Res*, *1*(1), 29–35.

Upadhyay, R. K. (2011). Plant natural products: Their pharmaceutical potential against disease and drug resistant microbial pathogens. *Journal of Pharmacy Research*, *4*(4), 1179–1185.

Upadhyay, S., Upadhyay, P., Vinode, R., & Dixit, V. K. (2013). Effect of ethanolic fraction of Hibiscus rosa sinensis l., leaves in androgenic alopecia. *Egyptian Dermatology Online Journal*, *9*(5), 2.

Urizar, N. L., & Moore, D. D. (2003). Gugulipid: A natural cholesterol-lowering agent. *Annual Review of Nutrition*, *23*(1), 303–313. doi:10.1146/annurev.nutr.23.011702.073102 PMID:12626688

Vaidyanathan, L., Thanikachalam, D., & Sivaswamy, L. T. (2014). Evaluation of wound healing potency of *Cassia auriculata* flower extracts using chick embryo wound model. *International Journal of Pharmaceutical Sciences Review and Research*, *27*(2), 222–227.

Valecha, N., Devi, C. U., Joshi, H., & Shahi, V. K. (2000). Comparative efficacy of Ayush-64 vs chloroquine in *Vivax* malaria. *Current Science*, *78*, 1120–1122.

Varma, N. (2016). Phytoconstituents and their mode of extractions: An overview. *Res. J. Chem. Environ. Sci*, *4*(2), 8–15.

Varsha, S., Agrawal, R. C., & Sonam, P. (2013). Phytochemical screening and determination of anti-bacterial and anti-oxidant potential of *Glycyrrhiza glabra* root extracts. *Journal of Environmental Research and Development*, *7*(4), 1552–1558.

Vasudevan, M., & Parle, M. (2009). Antiamnesic potential of *Murraya koenigii* leaves. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *23*(3), 308–316. doi:10.1002/ptr.2620 PMID:18844259

Vaughu, C., Gotto, A. J., & Basson, C. T. (2006). The evolving role of silymarin in management of atherosclerosis. *Journal of the American College of Cardiology*, *36*, 1–5.

Veerendra Kumar, M. H., & Gupta, Y. K. (2003). Effect of *Centella asiatica* on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. *Clinical and Experimental Pharmacology & Physiology*, *30*(5-6), 336–342. doi:10.1046/j.1440-1681.2003.03842.x PMID:12859423

Vijayasanthi, M., Kannan, V., Venkataswamy, R., & Doss, A. (2011). Evaluation of the antibacterial Potential of various solvent extracts of *Acacia nilotica* linn. leaves. *J. Drug Med*, *4*(1), 91–96.

Vinothapooshan, G., & Sundar, K. (2010). Wound healing effect of various extracts of *Adhatoda vasica. International Journal of Pharma and Bio Sciences*, *1*(4), 530–536.

Vinutha, J. P. (2007). Acetyl cholinesterase inhibitory activity of methanolic and successive water extracts of *Nardostachys jatamansi. International Journal of Pharmacology*, *23*, 127–131.

Vogel, H. A., & Pelletier, J. (1815). Curcumin-biological and medicinal properties. *Journal of Pharmaceutics*, *2*(50), 24.

Vollmar, A., Schfer, W., & Wagner, H. (1989). Immunologically active polysaccharides of *Eupatorium cannabinum* and *Eupatorium perfoliatum. Phytochemistry*, *25*(2), 377–381. doi:10.1016/S0031-9422(00)85484-9

Wagner, H., Proksch, A., Riess-Maurer, I., Vollmar, A., Odenthal, S., Stuppner, H., ... Heur, Y. H. (1984). Immunostimulant action of polysaccharides (heteroglycans) from higher plants. *Arzneimittel-Forschung*, *34*(6), 659–661. PMID:6541484

Wagner, K. H., & Elmadfa, I. (2003). Biological relevance of terpenoids. *Annals of Nutrition & Metabolism*, *47*(3-4), 95–106. doi:10.1159/000070030 PMID:12743459

Walsh, C. (2003). *Antibiotics: Actions, Origins, Resistance*. Washington, DC: ASM Press. doi:10.1128/9781555817886

Walsh, G., & Jefferis, R. (2006). Post-translational modifications in the context of therapeutic proteins. *Nature Biotechnology*, *24*(10), 1241–1252. doi:10.1038/nbt1252 PMID:17033665

Wang, F., Song, X., Ma, S., Liu, C., Sun, X., Wang, X., & Yu, Z. (2019). The treatment role of *Cyperus rotundus* L. to triple-negative breast cancer cells. *Bioscience Reports*, *39*(6), BSR20190502. doi:10.1042/BSR20190502 PMID:31123166

Wang, S., Zhu, Y., & Qiu, R. (2018). Shikonin protects H9C2 cardiomyocytes against hypoxia/reoxygenation injury through activation of PI3K/Akt signalling pathway. *Biomedicine and Pharmacotherapy*, *104*, 712–717. doi:10.1016/j.biopha.2018.04.144 PMID:29807220

Wang, Y., Hao, F., Nan, Y., Qu, L., Na, W., Jia, C., & Chen, X. (2018). PKM2 inhibitor shikonin overcomes the cisplatin resistance in bladder cancer by inducing necroptosis. *International Journal of Biological Sciences*, *14*(13), 1883–1891. doi:10.7150/ijbs.27854 PMID:30443191

Wang, Y., Jones, P. J., Ausman, L. M., & Lichtenstein, A. H. (2004). Soy protein reduces triglyceride levels and triglyceride fatty acid fractional synthesis rate in hypercholesterolemic subjects. *Atherosclerosis*, *173*(2), 269–275. doi:10.1016/j.atherosclerosis.2003.12.015 PMID:15064101

Watanabe, C. M. H., Wolffram, S., Ader, P., Rimbach, G., Packer, L., Maguire, J. J., & Gohil, K. (2001). The *in vivo* neuromodulatory effects of the herbal medicine *Ginkgo biloba. Proceedings of the National Academy of Sciences of the United States of America*, *98*(12), 6577–6580. doi:10.1073/pnas.111126298 PMID:11381109

Watanabe, S., Imanishi, J., Satoh, M., & Ozasa, K. (2001). Unique place of Kampo (Japanese traditional medicine) in complementary and alternative medicine: A survey of doctors belonging to the regional medical association in Japan. *The Tohoku Journal of Experimental Medicine*, *194*(1), 55–63. doi:10.1620/tjem.194.55 PMID:11556734

Waterman, P. G. (1993). Phytochemical dictionary: A handbook of bioactive compounds from plants. *Biochemical Systematics and Ecology*, *21*(8), 849. doi:10.1016/0305-1978(93)90098-C

Wealth of India. (2002). A Dictionary of Indian Raw materials and Industrial Products, National Institute of Science Communication, Council of Scientific and Industrial Research. New Delhi. *Raw Materials*, *10*, 100–107.

Weise, A., Altmann, F., Rodriguez-Franco, M., Sjoberg, E. R., Baumer, W., Launhardt, H., ... Gorr, G. (2007). High-level expression of secreted complex glycosylated recombinant human erythropoietin in the Physcomitrella D-fuc-t D-xyl-t mutant. *Plant Biotechnology Journal*, *5*(3), 389–401. doi:10.1111/j.1467-7652.2007.00248.x PMID:17359496

Wellwood, C. R. L., & Cole, R. A. (2004). Relevance of carnosic acid concentrations to the selection of rosemary, *Rosmarinus officinalis* (L.), accessions for optimization of antioxidant yield. *Journal of Agricultural and Food Chemistry*, *52*(20), 6101–6107. doi:10.1021/jf035335p PMID:15453673

White, N. J. (2004). Antimalarial drug resistance. *The Journal of Clinical Investigation*, *113*(8), 1084–1092. doi:10.1172/JCI21682 PMID:15085184

White, N. J. (2009). Malaria. In G. C. Cook & A. I. Zumla (Eds.), *Manson's Tropical Diseases* (22nd ed.). Elsevier.

WHO. (2002). *Traditional Medicine: Growing Needs and Potentials*. WHO.

WHO. (2014). *World Malaria Report*. WHO.

WHO. (2017). *Global priority list of antibiotic-resistant bacteria to guide research, discover, and development of new antibiotics*. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf

WHO. (2018). *World Malaria Report*. WHO.

Wildfeuer, A., Neu, I. S., Safayhi, H., Metzger, G., Wehrmann, M., Vogel, U., & Ammon, H. P. (1998). Effects of boswellic acids extracted from an herbal medicine on the biosynthesis of leukotrienes and the course of experimental autoimmune encephalomyelitis. *Arzneimittel-Forschung*, *48*(6), 668–674. PMID:9689425

Wilkinson, D., & Murray, J. i. (2001). Galantamine: A randomized, double-blind, dose comparison in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *16*(9), 852–857. doi:10.1002/gps.409 PMID:11571763

Willcox, M. L., & Bodeker, G. (2004). Traditional herbal medicines for malaria. *BMJ (Clinical Research Ed.)*, *329*(7475), 1156–1159. doi:10.1136/bmj.329.7475.1156 PMID:15539672

Williamson, E. M., Evans, F. J., & Wren, R. C. (1988). Potter's new cyclopedia of botanical drugs and preparations. Walden, UK: Saffron Walden.

Williamson, E. M. (2002). *Major herbs of Ayurveda*. Churchill Livingstone.

Wilson, D. N. (2014). Ribosome-targeting antibiotics and mechanisms of bacterial resistance. *Nature Reviews. Microbiology*, *1*(12), 35–48. doi:10.1038/nrmicro3155 PMID:24336183

Wilson, R. J., & Williamson, D. H. (1997). Extrachromosomal DNA in the Apicomplexa. *Microbiology and Molecular Biology Reviews*, *61*(1), 1–16. doi:10.1128/.61.1.1-16.1997 PMID:9106361

Woerdenbag, H. J., Lemstra, W., Malingre, T. M., & Konings, A. W. (1989). Enhanced cytostatic activity of the sesquiterpene lactone eupatoriopicrin by glutathione depletion. *British Journal of Cancer*, *59*(1), 68–75. doi:10.1038/bjc.1989.13 PMID:2757925

Wolinsky, L. E., Mania, S., Nachnani, S., & Ling, S. (1996). The inhibiting effect of aqueous *Azadirachta indica* (Neem) extract upon bacterial properties influencing in vitro plaque formation. *Journal of Dental Research*, *75*(2), 816–822. doi:10.1177/00220345960750021301 PMID:8655780

World Health Organization. (1999). *WHO monographs on selected medicinal plants.* WHO.

World Health Organization. (2000). *General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine*. Geneva, Switzerland: World Health Organization.

Wouters, K., Shiri-Sverdlov, R., van Gorp, P. J., van Bilsen, M., & Hofker, M. H. (2005). Understanding hyperlipidemia and atherosclerosis: Lessons from genetically modified apoe and ldlr mice. *Clinical Chemistry and Laboratory Medicine*, *43*(5), 470–479.

Wright, G. D. (2005). Bacterial resistance to antibiotics: Enzymatic degradation and modification. *Advanced Drug Delivery Reviews*, *57*(10), 1451–1470. doi:10.1016/j.addr.2005.04.002 PMID:15950313

Wu, Y. W., Tang, W., & Zuo, J. P. (2016). Development of artemisinin drugs in the treatment of autoimmune diseases. *Science Bulletin*, *61*(1), 37–41. doi:10.100711434-015-0975-9

Xiaoying, W., Han, Z., & Yu, W. (2017). Glycyrrhiza glabra (Licorice): ethnobotany and health benefits. In Sustained Energy for Enhanced Human Functions and Activity (pp. 231-250). Academic Press.

Xiufeng, P., Zhengfang, Y., & Zhang, X. (2009). Acetyl-11-Keto-β-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2–mediated angiogenesis. *Cancer Research*, *69*(14), 5893–5900. doi:10.1158/0008-5472.CAN-09-0755 PMID:19567671

Xu, A. H., Hu, Z. M., Qu, J. B., Liu, S. M., Syed, A. K. A., Yuan, H. Q., & Lou, H. X. (2010). Cyclic bisbibenzyls induce growth arrest and apoptosis of human prostate cancer PC3 cells. *Acta Pharmacologica Sinica*, *31*(5), 609–615. doi:10.1038/aps.2010.37 PMID:20418896

Xue, W., Hu, J. F., Yuan, Y. H., Sun, J. D., Li, B. Y., Zhang, D. M., & Chen, N. H. (2009). Polygalasaponin XXXII from *Polygala tenuifolia* root improves hippocampal-dependent learning and memory. *Acta Pharmacologica Sinica*, *30*(9), 1211–1219. doi:10.1038/aps.2009.112 PMID:19684611

Xu, X., Rajamanicham, V., Xu, S., Liu, Z., Yan, T., Liang, G., ... Wang, Y. (2019). Schisandrin A inhibits triple negative breast cancer cells by regulating Wnt/ER stress signalling pathway. *Biomedicine and Pharmacotherapy*, *115*, 108922. doi:10.1016/j.biopha.2019.108922 PMID:31048190

Xu, Y., Cao, Z., Khan, I., & Luo, Y. (2008). Gotu Kola (*Centella asiatica*) extract enhances phosphorylation of cyclic AMP response element binding protein in neuroblastoma cells expressing amyloid beta peptide. *Journal of Alzheimer's Disease*, *13*(3), 341–349. doi:10.3233/JAD-2008-13311 PMID:18431001

Yabuzaki, J. (2018). *Carotenoid Database*. Retrieved June 19, 2019, from http://carotenoiddb.jp/

Yabuzaki, J. (2017). *Carotenoids Database: Structures, chemical fingerprints and distribution among organisms. Database*. Oxford University Press.

Yadav, P., Verma, P., Khandelwal, N., & Prajapati, P. K. (2012). Clinical evaluation of kesharaja taila in the management of khalitya. *Endocrine*, *5*, 10.

Yadav, U. C. S., & Baquer, N. Z. (2014). Pharmacological effects of *Trigonella foenum-graecum* L. in health and disease. *Pharmaceutical Biology*, *52*(2), 243–254. doi:10.3109/13880209.2013.826247 PMID:24102093

Yakout, S. M., Abd-Alrahman, S. H., Mostafa, A., & Salem-Bekhit, M. M. (2013). Antimicrobial effect of seed ethanolic extract of Coriander. *Journal of Pure & Applied Microbiology*, *7*, 459–463.

Yakubo, S., Ito, M., Ueda, Y., Okamoto, H., Kimura, Y., Amano, Y., ... Watanabe, K. (2014). Pattern classification in kampo medicine. *Evidence-Based Complementary and Alternative Medicine*, 2014. PMID:24701241

Yamada, P., Isoda, H., Han, J. K., Talorete, T. P., Yamaguchi, T., & Abe, Y. (2007). Inhibitory effect of fulvic acid extracted from Canadian sphagnum peat on chemical mediator release by RBL-2H3 and KU812 cells. *Bioscience, Biotechnology, and Biochemistry*, *71*(5), 1294–1305. doi:10.1271/bbb.60702 PMID:17485833

Yamani, H. A., Pang, E. C., Mantri, N., & Deighton, M. A. (2016). Antimicrobial activity of Tulsi (*Ocimum tenuiflorum*) essential oil and their major constituents against three species of bacteria. *Frontiers in Microbiology*, *7*, 1–10. doi:10.3389/fmicb.2016.00681 PMID:27242708

Yan, L., Xiong, C., Xu, P., Zhu, J., Yang, Z., Ren, H., & Luo, Q. (2019). Structural characterization and in vitro antitumor activity of a polysaccharide from *Artemisia annua* L. (Huang Huahao). *Carbohydrate Polymers*, *213*, 361–369. doi:10.1016/j.carbpol.2019.02.081 PMID:30879680

Yan, W., Ma, X., Zhao, X., & Zhang, S. (2018). Baicalein induces apoptosis and autophagy of breast cancer cells via inhibiting PI3K/AKT pathway in vivo and vitro. *Drug Design, Development and Therapy*, *12*, 3961–3972. doi:10.2147/DDDT.S181939 PMID:30510404

Yersal, O., & Barutca, S. (2014). Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World Journal of Clinical Oncology*, *5*(3), 412. doi:10.5306/wjco.v5.i3.412 PMID:25114856

Yeung, S. C. S., Yao, S. C., & Wang, L. L. (1987). Pharmacology and Application of China Materia Medica (Vol. 2). Academic Press.

Yin, H., Huang, L., Ouyang, T., & Chen, L. (2018). Baicalein improves liver inflammation in diabetic db/db mice by regulating HMGB1/TLR4/NF-κB signalling pathway. *International Immunopharmacology*, *55*, 55–62. doi:10.1016/j.intimp.2017.12.002 PMID:29223854

Yogita, A., & Chandola, H. M. (2005). *Clinico-experimental study of Kushmandadi Ghrita in Generalized Anxiety Disorder (DSM-IV) wsr to Chittodvega* (Thesis). IPGT and RA, GAU, Jamnagar, Gujarat.

Yuen, M. F., Tam, S., Fung, J., Wong, D. H., Wong, B. Y., & Lai, C. L. (2006). Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: A 1-year prospective study. *Alimentary Pharmacology & Therapeutics*, *24*(8), 1179–1186. doi:10.1111/j.1365-2036.2006.03111.x PMID:17014576

Yu, F., Takahashi, T., Moriya, J., Kawaura, K., Yamakawa, J., Kusaka, K., ... Kanda, T. (2006). Traditional Chinese medicine and Kampo: A review from the distant past for the future. *The Journal of International Medical Research*, *34*(3), 231–239. doi:10.1177/147323000603400301 PMID:16866016

Yu, H. H., Lee, J. S., Lee, K. H., Kim, K. Y., & You, Y. O. (2007). *Saussurea lappa* inhibits the growth, acid production, adhesion and water insoluble glucan synthesis of *Streptococcus mutans.* *Journal of Ethnopharmacology*, *111*(2), 413–417. doi:10.1016/j.jep.2006.12.008 PMID:17234374

Yu, M.-S., Leung, S. K.-Y., Lai, S.-W., Che, C.-M., Zee, S.-Y., So, K.-F., & Chang, R. C.-C. (2005). Neuroprotective effects of anti-aging oriental medicine *Lycium barbarum* against β-amyloid peptide neurotoxicity. *Experimental Gerontology*, *40*(8-9), 716–727. doi:10.1016/j.exger.2005.06.010 PMID:16139464

Yu, Z. F., Kong, L. D., & Chen, Y. (2002). Antidepressant activity of aqueous extracts of *Curcuma longa* in mice. *Journal of Ethnopharmacology*, *83*(1-2), 161–165. doi:10.1016/S0378-8741(02)00211-8 PMID:12413724

Zadeh, J. G., Kor, Z. M., & Goftar, M. K. (2013). Licorice (*Glycyrrhiza glabra* Linn) as a valuable medicinal plant. *International Journal of Advanced Biological and Biomedical Research*, *1*(10), 1281–1288.

Zafar, R. (2009). *Medicinal Plants of India*. CBS Publishers and Distributors.

Zahara, K., Tabassum, S., Sabir, S., Arshad, M., Rahematullah, Q., Amjad, S. M., & Chaudhari, K. S. (2014). A review of therapeutic potential of *Saussurea lappa*- an endangered plant from Himalaya. *Asian Pacific Journal of Tropical Medicine*, *7*(1), 61–69. doi:10.1016/S1995-7645(14)60204-2 PMID:25312191

Zahid, A. M., Hussain, M. E., & Fahim, M. (2005). Antiatherosclerotic effects of dietary supplementations of garlic and turmeric: Restoration of endothelial function in rats. *Life Sciences*, *77*(8), 837–857. doi:10.1016/j.lfs.2004.11.039 PMID:15964306

Zahir, A. A., Rahuman, A. A., Kamaraj, C., Bagavan, A., Elango, G., Sangaran, A., & Kumar, B. S. (2009). Laboratory determination of efficacy of indigenous plant extracts for parasites control. *Parasitology Research*, *105*(2), 453–461. doi:10.100700436-009-1405-1 PMID:19308453

Zhang, A. H., Sun, H., Qiu, S., & Wang, X. J. (2013). Advancing drug discovery and development from active constituents of yinchenhao tang, a famous traditional Chinese medicine formula. *Evidence-Based Complementary and Alternative Medicine*. doi:10.1155/2013/257909 PMID:24191164

Zhang, H., Xie, B., Zhang, Z., Sheng, X., & Zhang, S. (2018). Tetrandrine suppresses cervical cancer growth by inducing apoptosis in vitro and in vivo. *Drug Design, Development and Therapy*, *13*, 119–127. doi:10.2147/DDDT.S187776 PMID:30587932

Zhang, W. X. (2003). Nanoscale iron particles for environmental remediation: An overvies. *J Nano Res*, *5*(3/4), 323–332. doi:10.1023/A:1025520116015

Zhang, W., Hong, R., & Tian, T. (2013). Silymarin's protective effects and possible mechanisms on alcoholic fatty liver for rats. *Biomolecules & Therapeutics*, *21*(4), 264–269. doi:10.4062/biomolther.2013.020 PMID:24244810

Zhang, Y. Q., Xu, J., Yin, Z. Q., Jia, R. Y., Lu, Y., Yang, F., ... Yi, G. (2010). Isolation and identification of the antibacterial active compound from petroleum ether extract of neem oil. *Fitoterapia*, *81*(7), 747–750. doi:10.1016/j.fitote.2010.03.015 PMID:20362038

Zhao, H. M., Gao, Z. W., Xie, S. X., Han, X., & Sun, Q. S. (2019). Withaferin A attenuates ovalbumin induced airway inflammation. *Frontiers in Bioscience*, *24*(3), 576–596. doi:10.2741/4737 PMID:30468675

Zhao, J., Yang, G., Liu, H., Wang, D., Song, X., & Chen, Y. (2002). Determination of andrographolide, deoxyandrographolide and neoandrographolide in the Chinese herb *Andrographis paniculata* by micellar electrokinetic capillary chromatography. *Phytochemical Analysis: An International Journal of Plant Chemical and Biochemical Techniques*, *13*(4), 222–227. doi:10.1002/pca.644 PMID:12184176

Zhao, T., Wang, X., Rimando, A. M., & Che, C. (1991). Folkloric medicinal plants: *Tinospora sagittata* var. cravaniana and *Mahonia bealei. Planta Medica*, *57*(05), 505–505. doi:10.1055-2006-960188 PMID:1798808

Zhao, Z., Jin, G., Ge, Y., & Guo, Z. (2019). Naringenin inhibits migration of breast cancer cells via inflammatory and apoptosis cell signaling pathways. *Inflammopharmacology*, *27*(5), 1021–1036. doi:10.100710787-018-00556-3 PMID:30941613

Zhao, Z., Liu, B., Sun, J., Lu, L., Liu, L., Qiu, J., ... Gong, W. (2019). Baicalein inhibits orthotopic human non- small cell lung cancer xenografts via Src/Id1 Pathway. *Evidence-Based Complementary and Alternative Medicine*, *2019*, 9806062. doi:10.1155/2019/9806062 PMID:30949224

Zheng, G. Q., Ho, D. K., Elder, P. J., Stephens, R. E., Cottrell, C. E., & Cassady, J. M. (1994). Ohioensins and pallidisetins: Novel cytotoxic agents from the moss *Polytrichum pallidisetum. Journal of Natural Products*, *57*(1), 32–41. doi:10.1021/np50103a005 PMID:7512623

Zheng, L., Hong, F., Lu, S., & Liu, C. (2005). Effect of nano-TiO_2 on strenght of naturally aged seeds and *growth of spinach. Biological Trace Element Research*, *104*(1), 83–91. doi:10.1385/BTER:104:1:083 PMID:15851835

Zhou, H. C., Wang, H., Shi, K., Li, J. M., Zong, Y., & Du, R. (2018). Hepatoprotective effect of baicalein against acetaminophen-induced acute liver injury in mice. *Molecules (Basel, Switzerland)*, *24*(1), 131. doi:10.3390/molecules24010131 PMID:30602693

Zhou, Z., Qi, H., Matsuda, N., Honma, I., Shimada, K., Takatsu, A., & Kato, K. (2004). Characterization of gold nanoparticles synthesized using sucrose by seeding formation in the solid phase and seeding growth in aqueous solution. *Journal of Physical Chemistry*, *108*(22), 7006–7011. doi:10.1021/jp035972i

Zito, P., Labbozzetta, M., Notarbartolo, M., Sajeva, M., & Poma, P. (2019). Essential oil of *Cyphostemma juttae* (Vitaceae): Chemical composition and antitumor mechanism in triple negative breast cancer cells. *PLoS One*, *14*(3), e0214594. doi:10.1371/journal.pone.0214594 PMID:30921428

Zuber, M., Rajesh, V., Anusha, K., Reddy, C. R., & Tirupathi, A. (2013). Wound healing activity of ethanolic extract of *Allium sativum* on alloxan induced diabetic rats family (Liliaceae). *International Journal of Science Inventions Today*, *2*(1), 40–57.

Zutshi, U., Rao, P. G., Kaur, S., Singh, G. B., Surjeet, S., & Atal, C. K. (1986). Mechanism of cholesterol lowering effect of Salaiguggal ex. *Boswellia serrata* roxb. *Indian Journal of Pharmacology*, *18*(3), 182.

About the Contributors

Manish K Dwivedi, Ph.D. scholar in the Department of Biotechnology, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh has completed his M.Phil. and M.Sc. in Biochemistry from Awadesh Pratap Singh University, Rewa, MP. He has been awarded gold medals during M.Sc. and M. Phil. His areas of interest are infectious disease biology and drug development. He has published several national and international papers.

Prashant Kumar Singh, Assistant Professor, Department of Biotechnology, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh has eleven years of research and seven years of teaching experience. He obtained his Ph.D. degree from JNU, New Delhi while working at CSIR-CDRI, Lucknow. His areas of research interest are Infectious disease biology and drug development. He has several research publications and research projects to his credit.

Ajeet Singh is currently working as Senior Researcher in ICAR-National Dairy Research Institute (ICAR-NDRI) Karnal, Haryana, India. He got his Bachelors and Masters in Microbiology from Chaudhary Charan Singh University Meerut (Uttar Pradesh) India. He has completed his Ph.D. in Microbiology from Gurukula Kangri University, Haridwar Uttarakhand India. He also qualified national eligibility test (NET) and Graduate Aptitude Test (IIT-GATE). He has awarded UGC-BSR (University Grants Commission-Basic Scientific Research, New Delhi) fellowship. He has published more than 40 research/review/popular articles and book chapters in reputed peer review national and international journals. He is an active reviewer of several national and international journals. He is an active life member of various national and international scientific societies and bodies. He is also working as a chief editor and assistant editor of various reputed journals.

Padam Singh belongs to Mathura, Uttar Pradesh, India. Currently, he is DST-SERB National Postdoctoral Fellow in DBT- Translational Health Science and Technology Institute, Faridabad India. He is working on to search novel scaffolds

active against drug-resistant and latent Mycobacterium tuberculosis. Before that, he worked for two months as Research Associate at ICAR-National Dairy Research Institute, Karnal, India. He completed his Doctorate in the year 2018 from CSIR-Central Drug Research Institute, Lucknow, India. During his doctoral work, he worked on drug discovery and development against tuberculosis and mycobacterial infection. He completed his Masters in Applied Microbiology in the year 2011 from Banaras Hindu University, Varanasi, India. He completed his bachelors in industrial microbiology from Dr. BR Ambedkar University, Agra, India. He has qualified GATE and CSIR-UGC NET in the year 2012.

Navneet Bithel is a Professor in the Department of Botany and Microbiology Gurukul Kangri University Haridwar, India. He earned M.Sc. and M.Phil. Degree in 1985 and 1987 respectively and Ph.D. in 1991 from Kurukshetra University, Kurukshetra. He joined Gurukul Kangri University Haridwar as Lecturer in 1992. He has been the Head of the Department of Botany and Microbiology from July 2013 to June 2016. He has guided 14 Ph.D. students and is supervising 5 research students on varied aspects of microbiology. He had been the Dean Student Welfare and Coordinator, National Service Scheme of Gurukul Kangri University. He has published over 100 research papers and reviews in National and International journals. Dr. Navneet is a Fellow of the Indian Botanical Society, Fellow of Indian Phytopathological Society and a life member of several academic societies.

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Tamilselvi Alagumuthu is a Sr. Principal Scientist in Centre for Human & Organisational Resources Development (CHORD), CSIR-Central Leather Research Institute, Adyar, Chennai – 600 020. She finished her PhD in the prestigious University of Madras, Chennai, India. Her area of interest is Leather biotechnology, Leather Microbiology, Fish Processing Technology, Development of fancy fish leathers including her specialization of Food Microbiology, Marine Biotechnology, and Fish Processing Technology. She has more than fourteen years of research experience. Further, she guided 26 M.Tech and 50 B.Tech students; she also published more than 40 research and review articles and also delivered her research findings in several national and international conferences. She visited Ethiopia and Turkey to share the research views. She received several grants from Government of India.

Sureshkumar Anandasadagopan is working as Scientist in Biochemistry & Biotechnology Laboratory, he completed his Ph.D in 2009 in the Department of Biochemistry, University of Madras, Guindy campus, Chennai. After his completion of doctoral degree he moved to University of Pennsylvania, USA for three years

to do his post-doctoral research studies on mitochondrial stress signaling and later he moved as visiting research fellow in University of Malaya, Kulalumpur, worked on the aspect of Natural products and drug discovery in cancer models. He joined CLRI in the year 2015 as Scientist. His research areas focused on Oxidative stress, Cell signaling, Cancer Biology, Natural products and drug discovery, Biomaterials in wound care management and Bone tissue engineering. So far he has published more than 25 research articles in Peer reviewed International journals and presented his findings in conferences and delivered invited lectures in various national seminars. He was also invited to review journal articles such as Journal of Nutritional Biochemistry (Elsevier), Journal of Injury (Elsevier), Journal of Parenteral and Eternal Nutrition, British Journal of Surgery (Wiley Publication), and Microscopy Research and Techniques (Wiley Publication). He currently has two project grants from DST-SERB and currently in his laboratory there two ongoing Ph.D students and he also completed desertion work for various project students.

Neelesh Babu earned B.Sc. Biotechnology Degree in 2012 from C.S.J.M. University Kanpur (Uttar Pradesh) and M.Sc. Microbiology Degree in 2014 from Gurukula Kangri Vishvavidyalaya, Haridwar, Uttarakhand, India. He qualified ICAR-NET in 2016. He was awarded by Rajiv Gandhi National Fellowship (Junior Research Fellowship) in 2017 and Senior Research Fellowship in 2019. Currently, he is perusing his Ph.D. from Gurukula Kangri Vishwavidyalaya Haridwar, Uttarakhand, India.

Priyanka is a senior PhD researcher in the Department of Biochemical Engineering and Biotechnology at Indian Institute of Technology Delhi, New Delhi, India. Her research expertise is on understanding the mechanism of quorum sensing among the microrganisms involved in plant growth regulation.

Aashaq Hussain Bhat is a DST Inspire Scholar, in Department of Zoology, Chaudhary Charan Singh University, Meerut. He is also working as a guest faculty in the Department of Environmental Science, in the same university and had also taught in Department of Biochemistry. He has done MSc. in Zoology with specialization as Parasitology and was topper of his batch. He has also done M.Phil. in Nematology and recently had submitted his PhD thesis. Mr. Aashaq Hussain Bhat has 7 years' experience in nematode taxonomy, microbiological bioinformatics, molecular biology and phylogenetics, evolution and biological control. He has reported several species of entomopathogenic nematodes for the first time from India and also described their associated bacterial symbionts first time globally. He has published 6 papers in well reputed international journals and many in UGC approved national journals. He has also published his findings in several proceedings/seminars. He has participated in 27 international / national seminars and has been facilitated with 5

best oral presentation awards. He has been invited two times for an invited talk at University of Allahabad and on time as External Resource Person for giving hands on training programme on Advanced Molecular Biotechniques at CSJM University, Kanpur. He has also served as a judge in 25th and 26th District Level National Children's Science Congress, Uttar Pradesh and one time in World's First Science Reality Show, Vigyan Ghar Season-2, Uttar Pradesh. He has also participated and presented paper in ESN 2018 at Ghent University, Belgium.

Rubina Chongtham has a PhD in Botany, specializing in transgenic crop improvement, plant-aphid interaction and Next Generation Sequencing. Has a strong interest in alternative means for crop protection and improvement. Also have a keen interest in exploring traditional knowledge of indigenous plants and their applications.

Ankita Gautam currently perusing Ph.D. in Biotechnology core subject Environmental Biotechnology from School of Biotechnology, Gautam Buddha University, Greater Noida, Uttar Pradesh (India). During 2012 interest developed towards different aspects of environmental problems in India, certainly biormediation and biodegradation became research of interest. During her M.Phil, she worked on "Bioremediation of polyaromatic hydrocarbons from fungal spp. isolated from contaminated soil". In 2016 during Ph.D. again started working on "Degradation and remediation of heavy metals and polyaroromatic hydrocarbons contaminated agriculture soil by *Trichoderma* spp. and other isolated fungal spp. near Hindon River" located at Ghaziabad, U.P. (India). Sustainable management of soil to enhance food crop quality and to overcome soil pollution is motive of research. Interested in contribution of knowledge through writing about different biological approaches related to human health benefits including environmental restoration.

Ahmad Hussain did his PhD and MSc from the Animal Biochemistry Division of National Dairy Research Institute Karnal, India. He did his graduation from Punjab University, Chandigarh, India. His research expertise is on in vitro and in vivo toxicity studies. His PhD research work was to evaluate toxicological impacts of nanofertilizers. Earlier he was Rajeev Gandhi Junior Research Fellow (DST-India) & currently he is a Senior Research Fellow in the National Dairy Research Institute Karnal, India.

Daraksha Iram is a Senior Ph.D Scholar in the Dairy Microbiology Division of National Dairy Research institute, Karnal, India, and she did her Master of Science in microbiology from Chaudhary Charan Singh University, Merrut in 2015. Her research work is on identification and designing of drug resistance antimicrobial peptide.

Javaria Kanwal is a lecturer of Chemistry on visiting basis in the Women University, Multan. She received BS (Hons) and M.Phil from Women University.

Sandeep Kumar obtained his PhD from the Animal Biochemistry Division of premier National Dairy Research Institute Karnal, India. He pursued his MSc in Biochemistry from Kurukshetra University. Currently Dr Sandeep is working as Senior Research Fellow in the Animal Biochemistry Division of National Dairy Research Institute Karnal, India.

Surbhi Mundra is DST INSPIRE Fellow in the Department of Molecular and Structural Biology Divisions, CSIR-Central Drug Research Institute, Lucknow, India. She has completed her masters in biotechnology from Sambalpur University, Sambalpur, Orisha. She has completed her bachelors from the same university in Zoology honors. Her area of interest includes antimicrobial resistance and structural biology.

Kiran Mustafa is a first-year Ph.D. student from Multan, Pakistan. She is currently serving as a Chemistry Lecturer in Higher Education Department (HED) Punjab, Pakistan. Her doctoral research investigates the synthesis and application of different materials ranging from organic and inorganic nanoparticles to synthetic membranes. She had worked on applications of magnetic nanoparticles, synthesis of antimicrobial compounds, polymer inclusion membranes, antimicrobial membranes, filtration membranes and on the extraction of phytochemicals from medicinally important plants. She takes a multidisciplinary approach that encompasses the fields of organic chemistry, physical chemistry, biochemistry, medicinal chemistry, and inorganic chemistry. She co-authored the articles like "Synthesis and Applications of Carbohydrate-Based Hydrogels" and "Pharmaceutical, Ethnopharmacological, Phytochemical and Synthetic Importance of Genus Aerva: A Review" also the "Comparative analysis of Sugars in Mangifera indica L. relative to quick decline disease". She has wide-ranging interests in scientific research including wound and burns healing technologies, superconductivity, solar panels, polymer modifications, alternate sources of food, etc.

Shahla Nigar is a DST Inspire Scholar, in Department of Animal Science, MJP Rohilkhand University, Bareilly-243006 (U.P.) India. She is working on cancer biology and toxicology of Fresh water fishes. She has published many national and international papers. She has attended many conferences and has won many awards and medals.

Saumya Pandey is currently working as Assistant Professor in department of Agriculture, Uttaranchal University, Dehradun, Uttarakhand (India). She has done her graduation and Post-graduation in Biotechnology from Banasthali Vidyapith, Rajasthan, India. She has completed her Ph.D. in biotechnology from Department of Bioscience and Biotechnology, Banasthali Vidyapith, Rajasthan (India). Her area of research is mainly molecular biology of plants and plant tissue culture. She has published her findings in peer reviewed journals of international repute as well as presented her work at different national and international conferences.

Ashok Kumar Pandurangan (Associate Professor), working in school of Life Sciences, B.S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur, Chennai, India. He finished his PhD in the prestigious Department of Biochemistry, University of Madras, Chennai, India during November,2011. He worked as a postdoctoral fellow in Centre for Cancer Research, Children's Hospital Oakland Research Institute (California, USA) in the field of S1PLyase deficiency on colitis associated cancer. Then he worked as postdoctoral fellow in Department of Nutrition and Dietetics, Universiti of Putra Malaysia, Serdang, Malaysia. Further he worked as a Visiting Research Fellow in the Department of Pharmacology, University of Malaya, Kuala Lumpur, Malaysia. He published over forty research and review articles in peer reviewed international journals and 5 book chapters. He also received grants in Malaysia and India.

Biljana Petrovic is associate professor at the Department orently works as a Reseaf Chemistry, Faculty of Science, University of Kragujevac, Serbia. She is teaching the following subjects: Advanced Inorganic Chemistry, The Chemistry of the Atmosphere, Mechanisms of Inorganic Reactions, and Inorganic Synthesis and Methods for Characterization. Her research work is based primary on kinetics and mechanisms of the substitution reactions of different transition metal ion complexes with biomolecules. She has published about 50 papers.

Snežana Radisavljević was born in Ćuprija, Serbia. She graduated from the Faculty of Science, University of Kragujevac at the Department of Chemistry, and got a Bachelor of Science degree. After bachelor studies, she has enrolled Master studies and graduated in June 2016. Now, she is a Ph.D. student in the field of Inorganic and Bioinorganic Chemistry.

Madhu Rani is presently working as Assistant Professor, Department of Botany, Deshbandhu College, University of Delhi, India. She studied B.Sc., M.Sc. (Botany), M.Phil. (Botany) from Chaudhary Charan Singh University, Meerut, India. She was awarded merit certificate for holding top rank in M.Phil. She was awarded Ph.D. in

2013. She qualified CSIR-UGC NET (JRF) in 2003 and availed JRF & SRF. She has won several awards in research papers and poster presentations in the phytoremediation, heavy metal stress in plants and cytology of millets. She has published research articles in reputed journals like Cytologia (Japan), Indian Botanical Society (India), and co-authored a book. Her areas of teaching and research interests are plant cytology, plant biotechnology, plant anatomy, plant resource utilizations, environmental studies, herbal medicine etc. She also served as a lecturer of M.Sc. (Botany & Industrial Biotechnology), in department of botany, CCS Univ. Merrut (India) during 2009-2011. She has teaching various courses to undergraduate students in the University of Delhi since 2012.

Manish Singh Sansi is a Senior PhD Scholar in the Animal Biochemistry Division of National Dairy Research institute Karnal, India. He did his Master of Science in Biochemistry from Central University of Rajasthan in 2015.His research expertise is on obesity induced changes in the cells with response to various kinds of internal and external signals.

Raghunath Satpathy received his M.Sc in Botany (with specialisation in Biotechnology) from Berhampur University science, India; (Post M.Sc.) Advanced P.G Diploma in Bioinformatics from University of Hyderabad and M. Tech. degree in Biotechnology from VIT University, Vellore India. He was awarded the degree for the doctor of philosophy (PhD) in Biotechnology by Sambalpur University, Odisha India. Currently he is working as an faculty member in the department of Biotechnology, M.I.T.S Engineering College Odisha, India. He is having more than 11 years of experiences in both teaching and research. He has authored many national and international journal papers, nine book chapters and one book to his credit. In addition to this Dr. Satpathy is associated with many professional bodies like ISRD, APCBEES, SCIEI, SABT, OBA. His current research interests include computational analysis of protein structure and environmental applications, data mining, biological database and analytical tool development. He is the recipient of many academic and research award such as: prestigious Adarsh Vidya Saraswati Rashtriya Puraskar (A national award of excellence from Global Management council, Ahmedabad, India), Senior Educator and Researcher award (A national award from National foundation for entrepreneurship development (NFED), Coimbatore, India), Best Teacher Award (IRDP group of Journals, Chennai, India), Best Young Teacher Award (Grace India Educational Charitable Trust, New Delhi, India, IRSD- Bright Researcher Award (Biotechnology) (Green ThinkerZ Society, Mohali, India) and Research Exllence award (IEAE Society, Karnataka).

Himani Sharma has completed her graduation from Daulat Ram College, Delhi University. She has joined the Chaudhary Charan Singh University for Masters in Zoology and she was a University topper in M.Sc Zoology. Then, she has completed her M.Phil under the supervision of Prof A. K. Chaubey from the Department of Zoology. Currently, she is pursuing PhD in Zoology from Chaudhary Charan Singh University.

Anuradha Singh (Assistant professor in Department of Chemistry, S S Khanna Girls' Degree College, University of Allahabad) recently completed a research project entitled "Design and Development of bi-functional Reverse Transcriptase Inhibitors of HIV Replication and Their Enhanced Cellular Uptake Using Myristoylated Derivatives" funded by the Department of Science and Technology (DST), New Delhi as Principal Investigator. Presently she is working as Principal Investigator in a start-up project funded by University Grants Commission, New Delhi. Her current research interest is focused around developing multifunctional anti-HIV, anti-HCV, anticancer and antibacterial agents. She is well versed in synthetic chemistry, computer-aided drug design and other techniques used in the field of medicinal chemistry. She has been awarded with gold medal during her post graduate studies and Swarnajayanti Fellowships by National Academy of Sciences, India. Dr. Singh has published more than 20 research papers/book chapters, in addition to several articles, in journals/ books of national and international repute.

Prashant Kumar Singh, Assistant Professor, Department of Biotechnology, Indira Gandhi National Tribal University, Amarkantak, Madhya Pradesh (India) has eleven years of research and seven years of teaching experience. He obtained his PhD degree from Jawaharlal Nehru Univ., New Delhi while working at CSIR-CDRI, Lucknow Uttar Pradesh (India). His areas of research interest are Infectious disease biology and drug development. He has several research publications and research projects to his credit.

Prathibha Sivaprakasam is a Research Scholar pursuing her Ph.D. in Bio-technology from the School of Life Sciences, B. S. Abdur Rahman Crescent Institute of Science and Technology, Chennai. She has completed her Masters from Annamalai University, Chidambaram and has 3 years of research experience as both Junior and Senior Research Fellow from Rajiv Gandhi College of Veterinary and Animal Sciences and Vector Control Research Center (ICMR), Pondicherry, respectively. During her research tenure she has one publication to her credit – "Immuno-Detection of C3a, a C3 Complement Activated Product in Mastitis Milk, a Potential Diagnostic Marker" in the journal 'Veterinary Sciences' in 2017. She is currently working in the field of Molecular Oncology, wherein her main focus is on testing the effects of

drugs on various signaling pathways in Triple Negative Breast Cancer, conducting both in-vitro and in-vivo studies.

Ashutosh Vats is a senior Ph.D. Scholar working in the Animal Biotechnology Center of National Dairy Research Institute, Karnal, India. He obtained his M.Sc. in Biotechnology from the CCS-Meerut University. His scientific expertise is in the field of Biotechnology and he is well-versed with current edge molecular biology tools.

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