Handbook of Research on

Advanced Phytochemicals and Plant-Based Drug Discovery

Ajeet Singh

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Handbook of Research on Advanced Phytochemicals and Plant-Based Drug Discovery

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ICAR-Indian Institute of Wheat and Barley Research, India

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surrounding subcontinents. Decoction is a basic Ayurvedic dose form that is one of the most commonly used and thought to be one of the most effective in traditional medicine. Plant ingredients are chopped into small pieces and soaked in a certain amount of water in an earthenware pot and other vessels to make decoctions. Polyherbal formulations, such as decoctions, have long been used in Ayurveda to treat a variety of ailments. It has been discovered that decoction can aid in the treatment and prevention of a variety of diseases, including neurodegenerative diseases, nasal diseases, allergic rhinitis, cancer, jaundice, liver disorders and metabolic diseases, cold pathogenic diseases, non-alcoholic fatty liver disease, and so on. This chapter delves into one of the oldest types of extractions utilized by our forefathers to treat a variety of ailments.

Chapter 3

Ethnoveterinary medicine is a branch of ethnobotany concerned with the study of traditional remedies. Ethnoveterinary methods are as old as domestication of numerous livestock species when it comes to animal healthcare. Herbal medicine has experienced a variety of conceptual modifications over time, yet its tone has stayed mostly same from antiquity to the present. Antibacterial, antifungal, insecticidal, and antioxidant action has been demonstrated for plants. Herbal treatment strives to not only cure the underlying cause of the illness, but also to reverse aberrant symptoms and restore the animals' health and vigour.

Chapter 4

This chapter tries to describe the most important plant extracts and their bioactive compounds which determine the antibiotic activity. Pharmacological assays performed for each plant extract are presented, including the minimum inhibitory concentration (MIC) as the most used experimental method to determine antimicrobial activity. Also, the effective associations between classic antibiotics and plant extracts with antibacterial are presented. The mechanisms of action are deeply explained to the extent that they are known and discovered by in vitro and in vivo studies. Plant-derived compounds have different mechanism of action as antibiotics. They can have other target sites than traditional antimicrobials and subsequently having different mechanisms of action against microbes. Ultimately, this chapter tries to be an invitation to use plant extract as an alternative to chemical, synthetic antibiotics, or used complementary, synergistic for better therapeutically results.

Section 2
Biological Activities of Medicinal Plants and Natural Bioactive Compounds

Humans have always been on the lookout for health-promoting drugs. Edible oils are one of the most well-known items for their nutritional and health benefits. This study looked at bioactive compounds in Moringa oleifera seed oil (MOSO) and its enormous potential use in the production of a variety of beneficial products. In fact, Moringa oleifera (MO) is cultivated for nutraceutical and medicinal utilities. Nevertheless, MOSO is now being researched for its possible application as a natural antioxidant for both edible and/or medicinal drugs. The effect of the different extraction techniques of seed oil and the origin of moringa seeds on the amount and quality of bioactive compounds were investigated in the present work. According to the findings, MOSO is a good source of nutrients and may be classified as a health-promoting product and can be used as a resource in the production of diverse culinary and medicinal items.

Edible oils are one of the important products that have lately come to light for their beneficial and nutritional properties. As a result, scientists and the oil industry are always working to demonstrate the health-giving benefits of both fruit and vegetable seed oils. Fruits are popular for their fleshy parts. However, the seeds are often discarded since they are thought worthless. This research looked at the bioactive components found in Cucurbitaceae (Cucurbita spp., Cucumis melo L., Citrullus lanatus) seed oils extracted using various extraction procedures on Cucurbitaceae seeds from various species and geographical places throughout the globe. The outcomes of the study show that Cucurbitaceae seed oils are a good source of nutrients and may be classified as health-promoting compounds. The discoveries have also cleared the way for the use of these seed oil resources in the production of a broad variety of therapeutic products.

Essential oils are terpinoids and their oxygenated derivatives, which are widely used for antimicrobial, fungicidal, antiparasitical, insecticidal uses. They are aromatic, hydrophobic, and volatile in nature and frequently used in medicinal and cosmetic industries. Especially nowadays, volatile oils have a significant role in pharmaceutical, sanitary, cosmetic, agricultural, and food industries. Various conventional and modern methods of extraction of volatile oil are available. Volatile oil can play an important role in minimization of microbial load at primary stage and/or to prevent the growth of the microorganisms during various stages of product management. However, there is still the need more emphasis on research regarding EO.

Section 3
Advanced Biological Technologies in Herbal Drug Discovery

In the modern era of science, nanotechnology has the ability to circumvent numerous disadvantages of conservative healing preparations. Important progress has been made towards the use of tailored nanomaterials (NMs) to treat the cancer with efficiency, specificity, and high sensitivity. Tailored NMs are operationalized with precise ligands that can predictably target the cancer cells and deliver encapsulated payloads meritoriously. Moreover, NMs can also be deliberated to increase the drug loading, controlled release, improved half-life, and selective distribution by altering their size, surface chemistry, composition, and morphology. The conservative cancer treatments have provoked the event and applications of nanomaterials. The emerging evidence suggests that nanomedicines will provide the next-generation stages for anticancer remedies.

Nanoparticles are currently being used rapidly and tested to overcome some of the limitations of standard drug delivery systems and can be used as an alternative treatment for cancer. These are the most important components of nanomedicine, and they have received much attention as promising programs for drug delivery and cancer treatment. Nanoparticles' ability to synthesize efficiently or by acting on demanded tissues or cells is the basis for implanted plant delivery systems. The primary goal of using nanoparticle-based technology was to improve drug solubility, bioavailability, absorption, and controlled release. In contrast to the last 50 years, nanoparticle-based drug discovery involves a high degree of uncertainty, and the production of pharmacologically active molecules from natural sources is not an alternative.

Preface

Phytochemicals are biologically active compounds present in plants used for food and medicines. A great deal of interest has been generated recently in the isolation, characterization and biological activity of phytochemicals. *Handbook of Research on Advanced Phytochemicals and Plant-Based Drug Discovery* is in response to the need for more current and global scope of phytochemicals and natural bioactive compounds. The topics covered in this book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The constantly changing landscape surrounding modern pharmacological and biomedical science makes it challenging for experts and practitioners to stay informed of the most up-to-date research. That is why the editor is pleased to offer this inclusive reference collection that will empower students, practitioners, academicians, and researchers with a strong understanding of various critical issues by providing both wide and comprehensive on cutting-edge theories and progress. This compilation is designed to act as single reference resource on conceptual, theoretical, methodological, and technical features as well as to provide insight into emerging trends and future prospective within the discipline.

Handbook of Research on Advanced Phytochemicals and Plant-Based Drug Discovery is planned into three sections that provide comprehensive coverage of important topics. The sections are:

1. Phytochemicals in Disease Management and Herbal Drug Discovery
2. Biological Activities of Medicinal Plants and Natural Bioactive Compounds
3. Advanced Biological Technologies in Herbal Drug Discovery

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

Chapter 1 discussed the several therapeutic utilization of bioactive compounds and phytochemicals. Bioactive compounds are compounds that are naturally extracted from plants and microbes. They are designated as energy-dense molecules because they play an important role in the normal functions and metabolic pathways of life.

Chapter 2 discussed the therapeutic aspects of herbal decoctions. Modern procedures and unique approaches to therapeutic modification get a boost from ethnic expertise. Ayurvedic medicine is a specialized form of traditional medicine that developed in India and the surrounding subcontinents. Decoction is a basic Ayurvedic dose form that is one of the most commonly used and thought to be one of the most effective in traditional medicine. Plant ingredients are chopped into small pieces and soaked in a certain

amount of water in an earthenware pot and other vessels to make decoctions. Polyherbal formulations, such as decoctions, have long been used in Ayurveda to treat a variety of ailments.

Chapter 3 discussed the therapeutic aspects medicinal plants and herbs for the management of various zoonotic diseases. Ethnoveterinary medicine is a branch of ethnobotany concerned with the study of traditional remedies. Ethnoveterinary methods are as old as the domestication of numerous livestock species when it comes to animal healthcare. For most of history, the growth of veterinary botanical medicine, the oldest kind of veterinary medicine, has followed a parallel path to that of human medicine. Herbal medicine has experienced a variety of conceptual modifications over time, yet its tone has stayed mostly same from antiquity to the present.

Chapter 4 describes the most important plant extracts and their bioactive compounds which determine the antibiotic activity. Pharmacological assays performed for each plant extract are presented, including the minimum inhibitory concentration (MIC) as the most used experimental method to determine antimicrobial activity. Also, there are presented the associations between antibiotics and plant extracts that have shown synergistic antibacterial activity against antibiotic-resistant bacteria.

Chapter 5 describes common neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's diseases and cognitive disorders originating from these are among the age-related diseases with the highest mortality rate. Our lifestyle, especially our eating habits, has effect on neuronal survival. New data show that improving dietary habits provides successful results in the prevention or treatment of diseases. The effective role of bioactive components on neuronal survival helps develop new therapeutic approaches.

Chapter 6 discuss the studies (*in vitro* or *in vivo*) reporting or suggesting the gut microbial effect on different phytochemicals. The gut microbiota plays an important role for host nutritional, physiological, immunological functions like food digestion, vitamin production, protection of gut integrity, regulation of host immunity and disease pathogenesis. Dietary phytochemicals are important factor to shape and change the human gut microbiota composition in diversity and abundance context. On the other hand, the microbial community of the gut provides a broad range of enzymes to host which are different from its own resources. This enables human gut microbiota to affect and direct the biosynthesis and metabolism of many bioactive compounds. Bioavailability of phyotchemicals is important to benefit from health conferring effects of these compounds.

Chapter 7 discusses the gastrointestinal diseases and their management using medicinal plants and bioactive compounds. This chapter also present some of the medicinal plants that are used to treat and minimize signals of GI disease pathogenesis. Gastrointestinal (GI) diseases are those that affect the digestive tract. This may include sections from the esophagus to the rectum, and the liver, gallbladder and pancreas associated digestive organs. Gastrointestinal diseases may be acute, chronic, or recurrent. Natural products show the potential ability to treat the causes and decrease the GI tract production systems.

Chapter 8 briefly highlights the current status of commercialized phytochemicals used as anticancer drugs along with mechanism of action of some important drugs. Cancer is one of the most deadly diseases caused due to abnormal division of the cells. Researchers are facing major challenge for finding the effective treatment of the cancer. Various methods of cancer treatment are chemotherapy, surgery, stem cell/bone marrow transplant, radiotherapy, hormone therapy and anticancer drugs. The anticancer drugs may be natural, semi-synthetic or synthetic in nature. The most widely used anticancer drugs are the phytochemicals isolated from the plants of their semi-synthetic analogues. So the research focuses on the isolation and identification of the bioactive compounds from natural sources as a potent anticancer agent.

Chapter 9 heighted the medicinal plants, and their bioactive compounds, utilized in diabetes therapy and molecular targets of Type 2 diabetes treatment. Type 2 diabetes (T2D) is a metabolic disorder related to persistent hyperglycemia. It is characterized by lack of secretion and/or reduce activity of insulin, which causes many chronic complications. Medicinal plants offer a passel of remedies that resolve symptomatology and mitigate the progression of T2D. Although several pre-clinical and clinical investigations indicate the success of conventional medicine in the prevention and treatment of diabetes, but still there are several side effects. Consequently, this necessitates the exploration of complementary and alternative treatment programs that may include natural products as safe and effective anti-diabetic candidates.

Chapter 10 focus on role of phytochemicals and natural products on major pathological factors in neurodegenerative diseases. Neurodegenerative illnesses are disorders that cause a considerable loss of neurons, both structurally and functionally, and affect millions of people globally. These disorders include Parkinson's disease, which is characterized by the loss of dopaminergic nigrostriatal neurons; Huntington's disease, characterized by the loss of spiny, medium-sized striatal neurons; and Alzheimer's disease (AD), characterized by cerebral atrophy. As a result of current therapeutic procedures and the progressive nature of these diseases, a number of side effects have emerged, prompting patients to seek alternative treatment.

Chapter 11 focuses on phytochemicals as antimicrobial agents, giving detailed information about infectious diseases and microbial agents responsible for the pathobiology of these diseases. Also, the mechanisms of antimicrobial activity of phytochemicals with antimicrobial properties were discussed. Microbial infections and antibiotic resistance are two of the most serious threats to society's health today. Millions of people die each year as a result of microbial infections. In 2020, the COVID-19 pandemic caused by viral infections was responsible for the highest amount of all deaths that year.

Chapter 12 focuses on the plant-based anticancer drug discovery. The number of people with cancer and death rates are constantly increasing in the world. Although surgery, radiotherapy and chemotherapy are still the most preferred methods, they have inadequacies, limited efficacy and side effects. Therefore, the development of new treatment methods has gained importance. Natural products were used for medical and therapeutic purposes in ancient times and are still used today. While some naturally derived molecules have already been shown to be effective against cancer, studies are ongoing for many natural molecules as cancer therapeutics. There are still many plant species and compounds whose effectiveness has not yet been discovered in the world.

Chapter 13 focuses on the several medical aspects of *Moringa oleifera*. Humans have always been on the finding out for health-promoting drugs. Edible oils are one of the most well-known items for their nutritional and health benefits. This study looked at bioactive compounds in *Moringa oleifera* seed oils (MOSO) and its 'enormous potential use in the production of a variety of beneficial goods. In fact, *Moringa oleifera* (MO) is cultivated for nutraceutical and medicinal utilities. Nevertheless, MOSO is now being researched for its possible application as a natural antioxidant for both edible and/or medicinal drugs. The effect of the different extraction techniques of seed oil and the origin of moringa seeds, on the amount and quality of bioactive compounds were investigated in the present work. According to the findings, MOSO is a good source of nutrients and may be classified as a health-promoting product and can use as resource in the production of diverse culinary and medicinal items.

Chapter 14 focuses on bioactive compounds of Cucurbitaceae seed oils as nutraceuticals and health promoting activities. Edible oils are one of the important products that have lately come to light for their beneficial and nutritional properties. As a result, scientists and the oil industry are always working to demonstrate the health-giving benefits of both fruit and vegetable seed oils. Fruits are popular for their

fleshy parts. However, the seeds are often discarded since they are thought worthless. This research looked at the bioactive components found in the Cucurbitaceae (*Cucurbita* spp., *Cucumis melo* L., *Citrullu slanatus*) seed oils extracted using various extraction procedures on Cucurbitaceae seeds from various species and geographical places throughout the globe. The outcomes of the study show that Cucurbitaceae seed oils are a good source of nutrients and may be classified as health-promoting compounds.

Chapter 15 deals with the therapeutic aspects of rosmarinic acid. Rosmarinic acid is a valuable polyphenolic molecule mainly found in species of Boraginaceae and Lamiaceae. The amount of Rosmarinic acid varies according to the environmental condition in which the plant grows, temperature and humidity. The content of 0.01 to 72 mg/g Rosmarinic acid has been determined in various plants. Biotechnological production of Rosmarinic acid by plant cell culture is recommended for its high production. The investigations have mainly addressed sources of Rosmarinic acid, its production and biological effects. Rosmarinic acid is a valuable molecule with antioxidant, anti-inflammatory, antiviral, and anticancer activities. Since Rosmarinic acid has a broad biological spectrum, it is an important substance for the pharmaceutical, food and cosmetic industries. In addition to its antioxidant effects, it has been tested in recent studies in neurodegenerative diseases and has been found to have beneficial effects in these diseases, especially on memory.

Chapter 16 focused on the importance of arugula (*Eruca sativa*) and pharmacological effects of different phytochemical Rocket salad (*Eruca sativa*), a member of the Brassicaceae family, is an important vegetable for human health because of its antioxidant, anti-inflammatory, anticancer, antiproliferative, and antiangiogenesis properties, as well as its rich chemical composition. Important phytochemical substances in rocket salad, including flavonoids and glucosinolates, have an important function in human health protection. These components can scavenge free radicals, reduce lipid peroxidation, and have anticancer effects by activating apoptosis in cancer cells.

Chapter 17 describes the overview of extraction, isolation and bioavailability aspects of Resveratrol. The phytochemistry and Bioavailability of ResveratrolNatural products derived from plants have long been and will continue to be substantial sources of therapeutic agents in disease prevention and treatment. Resveratrol, which is a bioactive compound in a polyphenol structure, is found in significant amounts in several plant/food sources such as grapes, peanuts, strawberries, blueberries, pistachios, red mulberry, cranberries, and tomatoes. These functional foods rich in resveratrol be used widely owing to resveratrol does not show significant toxicity at low doses. Today, there is an increasing interest in polyphenols due to their antioxidant properties. The antioxidant effect of resveratrol underlies many of its medicinal effects, such as its neuroprotective and positive effect on neurodegeneration. In addition, it is outstanding with anti-inflammatory, antitumor, antiviral, antidiabetic, cardioprotective, and life-prolonging effects.

Chapter 18 highlights the research-based analysis of potential antiviral compounds from the plants in the mangrove ecosystem. Phytochemicals are recently gaining major attention for their therapeutic uses against several pathogenic viruses. Hence, searching for novel antiviral molecules from plant sources is desirable as it is having fewer side effects. The mangrove plants are considered as an excellent source of phytomedicine due to production of several classes of phytochemicals. However, fewer studies have been conducted regarding the extraction of the potential antiviral compounds from mangrove sources. In this chapter, an overview of isolation, extraction and qualitative estimation of phytochemicals from the mangrove plants have been described.

Chapter 19 begins with a brief description of carcinogenesis, the important events associated with carcinogenesis such as what lead a normal cell to transform into a pre-neoplastic one, their multiplication and development into cancer. It was described how carcinogens are metabolised into reactive oxygen

species (ROS) endogenously, and how they cause DNA cleavage and base oxidation generating mutations and accumulation of such mutations leading to gene activation or suppression and the role of inflammation in cancer. Elucidation of how cancer arises contributes to our ability to understand the molecular mechanisms of action of some natural products. Herbal natural products contain secondary metabolites that exert a physiological effect within the human body. These metabolites are used therapeutically in modern medical practices to prevent and cure various diseases including cancer. This chapter discusses the anticancer property of *Aristolochia tagala* and *Curcuma caesia* in chemically induced liver cancer of mice and describes the most probable molecular mechanisms of action of the metabolites present in these plants contributing to their anticancer effect.

Chapter 20 summarizes EOs, its relevant components, extraction methods, their biological importance and antimicrobial fumes. Essential oils are terpenoids and their oxygenated derivatives, widely used as antimicrobial, fungicidal, antiparasitic, insecticidal, etc. They are aromatic, hydrophobic and volatile in nature and frequently used in medicinal and cosmetic industries. Nowadays, volatile oil have significant role in pharmaceutical, sanitary, cosmetic, agricultural and food industries. Various conventional and modern methods of extraction of volatile oil are available.

Chapter 21 summarizes essential oils, its components, extraction methods, and their therapeutic importance. Essential oils are plant derived secondary metabolites that find immense application in the treatment and management of both communicable and non-communicable diseases. These oils exert a wide array of pharmacological and biological properties that are attributed to the various classes of its phytoconstituents. As these phytoconstituents act on multiple cellular targets they are found to be beneficial in wide range of diseases. To overcome the bottlenecks in allopathy medication and also to minimize their adverse effects, alternative therapies utilizing essential oils and their components gained momentum which are found to be safe, available and affordable. The myriad components of essential oil offer potential lead compounds in the drug discovery process. As many of essential oils and their components are in phase III clinical trials, drugs derived from them will protect and promote health and welfare of mankind.

Chapter 22 is a series of biological NMs that is presently being working for the anticancer healings and converse the central role of their biological possessions in the cancer remedy. In the modern era of science nanotechnology has the budding to circumvent numerous disadvantages of conservative healing preparations. Several important progresses have been prepared towards the use of tail or head nanomaterials (NMs) to treat the cancer with efficiency, specificity, and high sensitivity. Tailored NMs operationalized with precise ligands that can predictably target the cancer cells and deliver encapsulated payloads meritoriously. Moreover, NMs can also be deliberated to increase the drug loading, controlled release, improved half-life, and selective distribution by altering their size, surface chemistry, composition, and morphology. The conservative cancer treatments existing natural boundaries have provoked the event and applications of nanomaterials, which compromised with a hopeful and harmless dealing. The emerging evidence suggests that nanomedicines will provide the next-generation stages for anticancer remedy.

Chapter 23 describes the nanoparticles-based targeted drug delivery for effective cancer management. Cancer is one of the most serious diseases. Nanoparticles are now being rapidly used and trialed to overcome few limitations of traditional drug delivery systems and are also serves as a distinct therapeutics for the treatment of cancer disease. These are the main component of nano-medicine and also a promising system of drug-delivery for diagnosis of cancer and therapy. Initially, the use of nanoparticles based technology was depended on increasing the solubility of a substance, bioavailability, and drug absorption and regulated release. Although developing chemicals particularly pharmacological active

from natural resources are no longer preferred alternative, as it was fifty years ago, boosting the effectiveness of naturally bioactive substances with nanoparticles has become a prevalent characteristic.

Chapter 24 discuss the bioactive compounds as well as the mechanisms of active substance release and drug delivery routes. Drugs with low bioavailability (e.g., hydrophilic therapeutics) are often administered by injection. Bioactive compounds of plant origin are used all over the world because of their positive impact on human and animal health and because of their beneficial, specific properties. The most popular bioactive compounds beneficial to health have been identified and defined earlier, others are yet to be discovered. In particular, the most common biological activities of these compounds were indicated, such as: antiallergic, antidepressant, antidiabetic, anti-inflammatory, antimicrobial, antitumor, antiviral, antithyroid, anxiolytic, to cardioprotective, hepatoprotective and flatulence inhibiting effects. The beneficial properties of bioactive compounds may be associated with substances like alcohols, terpenoids, phenolic antioxidants and rosmarinic acid, which are present in several medicinal plants.

Chapter 25 give an overview of the essential aspects of bioavailability and bio accessibility of phytochemicals, components restricting the oral bioavailability of the phytonutrients and the mechanisms responsible for the absorption and metabolism of bioactive compounds. The chapter will also discuss some of the recent delivery systems that can be accessed to improve the bioavailability of bioactive compounds by several folds. Phytochemicals or phytonutrients, are chemicals produced naturally by plants for protection and prevention from diseases. Bioactive compounds are found in fruits, vegetables, whole grains etc. including a heterogeneous class of compounds (polyphenolic compounds, organosulfates, tocopherols, carotenoids, and phytosterols) ranging between a wide range of chemical structures (lipophilic or hydrophilic), natural diversity (ubiquitous or specific), possible action site, concentration range both in human body and food matrix, efficiency against oxidative damage, biological activity, and specificity. Various aspects like sources, biomolecules present in the food and chemical interactions with other phytochemicals interfere with the bioavailability of these bioactive compounds. Several other factors drastically affecting the oral bioavailability of phytochemicals include controlled discharge of bioactive components from food matrix, their solubility in gastric juice, absorption through intestinal epithelial cells, and chemical or enzymatic reactions taking place in the digestive system. Studies on potent health benefits of phytochemicals and methods to enhance their bioavailability are still much in inception.

As a comprehensive collection on the latest findings related to biomedical sciences, computational biology and bioinformatics, botany, Herbal drug discovery, microbial diseases and their herbal management, essential oils based-herbal therapeutic drugs, pharmacological uses of medicinal plants and natural bioactive compounds etc. “Advanced Phytochemicals and Plant-based Drug Discovery”, 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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ICAR-Indian Institute of Wheat and Barley Research, India

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Section 1

Phytochemicals in Disease Management and Herbal Drug Discovery

Chapter 1
Therapeutic Utilization of Bioactive Compounds and Phytochemicals:
A Current Scenario and Future Prospective

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ABSTRACT

Bioactive compounds are compounds that are naturally extracted from plants and microbes. They are designated as energy-dense molecules because they play an important role in the normal functions and metabolic pathways of life. Not all bioactive compounds have positive impacts on pathways, and some have negative consequences as well. It has been observed that these derived bioactive compounds possess remarkable characteristics such as healing, anti-cancerous, anti-oxidant, etc. Phytochemicals are the bioactive compounds that are present in foods and possess the ability to interfere positively with the metabolism of human health. They have been classified as alkaloids, terpenoids, phytosteroides, resveratrol, and cardiac glycosides. It has been observed that these bioactive compounds are the center of attraction in the drug discovery areas which are utilized against various diseases as plants and microbes are exploited for the extraction of bioactive compounds.

INTRODUCTION

Bioactive compounds are compounds that are naturally extracted from plants and microbes. The term

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'bioactive' comprises two words i.e., 'bios' and 'activus' which refer to compounds having the ability to provide energy to humans. They are designated as energy-dense molecules because they play an important role in the normal functions and metabolic pathways of life. Not all bioactive compounds have positive impacts on pathways, and some have negative consequences as well. Besides this, several bioactive compounds have both positive and negative effects on the metabolic pathway. The positive and negative effects of bioactive compounds are determined by their in the body. Though, their concentration is also dependent on so many factors such as the nature of the compound, components of compounds, their interaction with the other molecules or substances, etc. It has been observed that these derived bioactive compounds possess remarkable characteristics such as healing, anti-cancerous, anti-aging, antipyretic, etc. (Huang *et al.,* 2010; Bendary *et al.,* 2013; Nath *et al.,* 2013). There are some essential bioactive molecules which have been required by the body in order to develop resistance against various disorders (Biesalski *et al.,* 2009). There are some non-essential bioactive molecules whose presence increases the metabolism but their absence doesn't have any consequences (Biesalski *et al.,* 2013). The essential bioactive molecules comprises of vitamins, fatty acids which plays important role in metabolic pathways. Some of the vitamins are required by the enzymes as cofactors. Though they are considered beneficial for human health, still, consumption of these compounds beyond the prescribed doses can cause adverse effects also (Chambial et al., 2013). Phytochemicals are the bioactive compounds that are present in foods and possess the ability to interfere positively with the metabolism of human health. They are the non-essential compound which shows diversity in structure and function (Biesalski *et al.,* 2009). They have been classified as alkaloids, terpenoids, phytosteroides, and cardiac glycosides (Somani *et al.,* 2015). It has been observed that these bioactive compounds are the center of attraction in the drug discovery areas which are utilized against various diseases as plants and microbes are exploited for the extraction of bioactive compounds. Phytochemicals are the ones which are mostly present as active compound or secondary metabolite in the plants. There are primary and secondary metabolites in the plants. Primary metabolites are those compounds which are required by the plants for their survival purposes (Akhtar *et al.,* 2019; Omeroglu *et al.,* 2019). On the contrary, secondary metabolites are the ones which have been used by the plants for their defense purposes (Zhang *et al.,* 2015; Cooper & Nicola, 2015).

MAJOR PHYTOCHEMICALS

Alkaloids

These are one of the classes of secondary metabolites processed by the plants. The basic structure of alkaloids comprises of the nitrogen group. The presence of nitrogen group in the place of hydrogen characterizes it under alkaloids. They possess the antimicrobial and anti-analgesic effects. The antimicrobial activity of these compounds came into light when it has been observed that they enhance the activities of WBCs (White Blood Cells). Due to the enhance activity of the WBCs, microorganism clearance increases in the cell (Ogunwenmo *et al.,* 2007). The other alkaloids found to be complex in structure which involves the aromatic alkaloids. They target the genetic material of the organisms and like ethidium bromide; they are also involved in the intercalation along with the cell wall (Cowan, 1999). The most commonly used alkaloids have multifaceted role in the medicine field. They are known to act as antimalarial, anti- depressant, anti antineoplatic activities and many more (Ngoci *et al.,* 2011). The utilization of the alkaloids is not limited to these activities only. Besides this, they are involved in the

treatment of various diseases. They have the potential to stimulate various known and important neurotransmitters at the junction where a muscle and neuron passes down the signal with the help of these neurotransmitters (Ngoci, *et al.,* 2011). They are also helpful in reducing the pain cycles which frequently arouses in different conditions such as wounds, pain in the abdomen etc. (Ngoci *et al.,* 2011). Cancer is one of the diseases where metastases become a major problem in the malignant tumor. There are various drugs and chemicals have been exploited in the chemotherapy to restrict the growth of the tumor. The alkaloids also play important role in the treatment of cancer mainly leukemia and Hodgkin's disease. As mentioned earlier, the dose of the phytochemicals is very crucial in deciding the adverse and beneficial effects. Though, they are very useful for the metabolic activities and other properties which provide benefits to human society. It has been seen that some of the alkaloids are not good for the metabolic purposes and they possess negative effects on the health (Ogunwenmo *et al.,* 2007; Ngoci *et al.,* 2011).

Tannins

One of the classes of polyphenols is tannins. The basic structure of tannins consists of the phenolic ring and they are classified into two categories i.e., hydrolysable and condensed. The hydrolysable tannins have been obtained by the action of gallic acid on the tannins. The –OH group present on the tannins undergo esterification process by the gallic acid (Al Mamari, 2021). On the contrary, the tannins which don't undergo hydrolysis reactions are termed as condensed tannins. As their name suggests they are formed from the condensation reactions (H. Al Mamari, 2021). The major difference between the two categories which leads to the classification is that hydrolysable tannins can be easily degraded by the action of acids as they can be hydrolyzed. However, the condensed tannins doesn't degraded that easily as they can't be hydrolyzed by the acids. The condensed tannins possessed the antioxidant activities and found to be involved in many other reactions such as restricting the oxidative enzymes and many more (Navarro *et al.,* 2003; Vit *et al.,* 2008; Ngoci *et al.,* 2011). Various studies also suggest the role of tannins in inhibiting the growth of tumor. They target the cell death pathway commonly known as apoptosis. In cancer cells, it has been observed that all the factors and enzymes responsible for natural cell death found to be down regulated which helps growing tumor. Tannins work towards the stimulation and enhancement of the apoptosis, so that tumor growth can be reduced or inhibited (Scalbert *et al.,* 2005).

Tannins also functions as anti- microbial agent. The microorganisms in order to develop infection require attachment with the host which in turn needs adhesion proteins. These adhesion proteins have been targeted by the tannins and sometimes, they also disrupt the membrane which leads to either prevention from the infection or death of the microorganism (Cowan, 1999; Okuda, 2005; Biradar *et al.,* 2007; Ngoci *et al.,* 2011). To inhibit the microbe's infection, they extend their functions beyond the disruption of cell wall or cell wall proteins. It has been seen that tannins gather those metal ions which are requisite for the development of microbes. As some of the factors required for the attachment, some of them necessarily work on the growth and many more. Reverse transcriptase is the enzyme which is utilized by the viruses especially retroviruses for integrating its genetic material into the host genome. The enzyme catalyzes the reverse transcription reaction where DNA has been obtained from the mRNA. This enzyme is also targeted by the tannins which restricts its activity (Okuda, 2005; Biradar *et al.,* 2007; Ogunwenmo *et al.,* 2007; Ngoci *et al.,* 2011). It is been interesting to know that the susceptibility of the microorganism towards the tannins infection increases with the increment in the number of –OH group (Przybylski *et al.,* 1998; Cowan, 1999; Biradar *et al.,* 2007; Samy & Gopalakrishnakone, 2008; Ngoci *et al.,* 2011). Hormones play major role in the growth and development of the body and they can travel

distant sites as they are released from the ductless glands. They also play important in signaling. Tannins, despite of all toxic effects to the microbes, also act in this system where they target the receptors of the estrogen. They are found to be lethal to many mollusks, as a result of which they are highly exploited in the controlling the infection of the Schistosomiasis. This infection is caused by the trematode parasite known as *Schistosoma* spp. and its life cycle involves the definitive and intermediate hosts as humans and mollusks, respectively. They are also used in curing the diarrhea, fungus and parasitic infections along with arterial clearance (Awoyinka *et al.,* 2007; Ogunwenmo *et al.,* 2007; Ngoci, *et al.,* 2011).

Flavonoids

The basic structure of flavonoids comprises of 15 carbons forming a C6-C3-C6 compounds. The carbons are attached to the benzene rings and other flavonoids structure derived from the modification in the basic structure. The presence of the sugar moieties increases the solubility of these compounds in water (Harborne, 1973). Like all other secondary metabolites, they are helpful in reducing the oxidative stress. The oxidative stress also produced from the Low-density lipoprotein. The increasing amount of bad cholesterol also found to be harmful for the heart. The metabolic processes carried out to decrease the oxidative stress seem to be favored in the presence of flavonoids especially the quercetin (Ngoci, *et al.,* 2011). They play an important role in the elimination of those compounds which possess the capability of inducing mutation or cancer. Both are serious for the body as mutations are one of the factors in developing cancer (Ogunwenmo *et al.,* 2007; Ngoci *et al.,* 2011). These compounds also restrict the growth of the microorganism. They inhibit the growth either by inhibiting the protein required for the attachment to the host or by interfering with their membrane (Navarro et al., 2003; Al-Bayati & Al-Mola, 2008; Samy & Gopalakrishnakone, 2008; Kaur & Arora, 2009; Ngoci *et al.,* 2011).Most of the drugs derived from this have been recommended to the patients of blood pressure as it lowers the pressure and decrease the muscles heavy utilization of the oxygen (Dong *et al.,* 2005; Ngoci *et al.,* 2011). The consumption of these bioactive molecules has been extended where allergies, spasms and other diseases such as asthma also treated (Ngoci, et al., 2011). Though, most of the flavonoids derivatives have the potential to restrict the growth of various disease caused by the microorganism, still, it has been observed that presence of the alcohol group in the structure increases the efficacy of flavonoids derivatives against the microorganism in comparison to those which lacks the group (Cowan, 1999; Samy & Gopalakrishnakone, 2008; Ngoci *et al.,* 2011).

Saponins

They are present in the leguminous plants. The name saponin derived from the characteristics of the compounds which have the ability to make foams when come in contact with an aqueous solution like soap. The other noticeable characteristic of saponin is the damage to blood cells which gets hemolysed in the presence of these compounds (Harborne, 1973).Their characteristics have been exploited in treating the cough as they induce the release of the sputum through the natural openings such as nose and mouth. Like all other bioactive molecules, they are also possess the ability to restrict the growth of microorganism especially protozoa. The protozoan consists of the cholesterol molecules which are the targets of saponins. Every biological membrane requires cholesterol but this has been disrupted by the saponins which becomes fatal for the protozoa. The adjuvants play an important role in promoting the immune response. The role of saponins as adjuvants becomes useful in the vaccines (Ngoci *et al.,* 2011).

They inhibit the growth of the bacteria by utilizing their properties in which they lyse the membranes of the bacteria. Besides this, the reaction in the extracellular medium increases which makes the bacteria more susceptible for killing. This is also occurred due to the saponin property of reducing surface tension (Al-Bayati & Al-Mola, 2008).

The drugs derived from the saponin also inhibit the cancer cells invasiveness. The normal cells didn't harm from this drugs as they target cholesterol of cancer cells membrane. The reaction leads to the induction of various checkpoints which promotes the arrest and promotes the cell death (Ngoci *et al.,* 2011). It has been seen that the bacteria responsible for the colon cancer has been inhibited by the saponins (Ngoci, *et al.,* 2011). It has been found that saponin also possesses the ability to reduce to blood pressure which prevents most of the heart problems. Likewise, it has been observed that in the presence of saponins, there is a decrement in the demand of oxygen by the myocardial muscles (Dong *et al.,* 2005).

Phytosteroids

This is one of the hormones or bioactive molecules which shares similarity with the animal hormones. The basic structural similarity between the two has been observed with the contrasting side groups which them different from each other (Ngoci *et al.,* 2011). Due to their structural similarities with the animal hormones, they have been used in the pregnant women for the comfortable delivery without complications. Furthermore, they are prescribed to women for increasing the fecundity. They also exploited for increasing the sex drive in males. Various artificial sex hormones could be prepared from this due to the structural similarity. They are mostly prescribed at the time of contraception (Edeoga *et al.,* 2005; Ngoci *et al.,* 2011). The uses of these steroids didn't stop here as they are exploited for treating diseases caused by microorganism, inflammation and extending their properties to cure stomach related problems. They have been reported for reducing the levels of the bad cholesterol which is harmful for the heart (Ngoci *et al.,* 2011). They inhibit or suppress the immune responses which in some patients have been exaggerated leads to various problems. The drug derived from the phytosteroids is physalins utilized to treat those immune responses (Soares *et al.,* 2005; Ngoci *et al.,* 2011).

Terpenoids

Isoprene unit has been derived from the Isopentenyl diphosphate (IPP) and terpenoids derived from the isoprene. They share similar basic structure with differences in the adjoining groups (Harborne, 1973). They have been used for treating the diseases caused by the fungus, virus, bacteria and protozoa. They, in contrast to phytosteroids, have known to boost the immune systems of the humans. The action of these compounds on cancer cells is commendable as they restrict the invasion without harming the normal body cells (Roberts, 2007; Ngoci *et al.,* 2011).Their uses doesn't end here, but, the invasion of the microorganisms also limited by them. It has been evident from the studies that they target the membranes of these microorganisms which are the base of attachment (Cowan, 1999; Ogunwenmo *et al.,* 2007; Samy & Gopalakrishnakone, 2008; Ngoci *et al.,* 2011). Furthermore, if membranes have been disturbed then the composition and permeability also gets affected. Sometimes, they are disturbed to that level where the intracellular material comes out to exterior. The other possible reason came into existence suggested that interaction between the phytochemicals and the interior materials of the cell serves as the bacterial inhibitor sites (Trombetta *et al.,* 2005). They are also used to treat epilepsy and other viral borne diseases along with curing the diseases of the lungs (Ngoci *et al.,* 2011). The in vitro studies demonstrated

that the terpene derived from the Ginseng interacts with the master gland and hypothalamus along with adrenal glands. This fact has been established by observing the levels of hormones in the blood. The axis which controls all the hormones has been targeting by the derivatives. There is a rise in adrenal cortex hormone levels which have been regulated by the axis only (Briskin, 2000; Ngoci *et al.,* 2011).

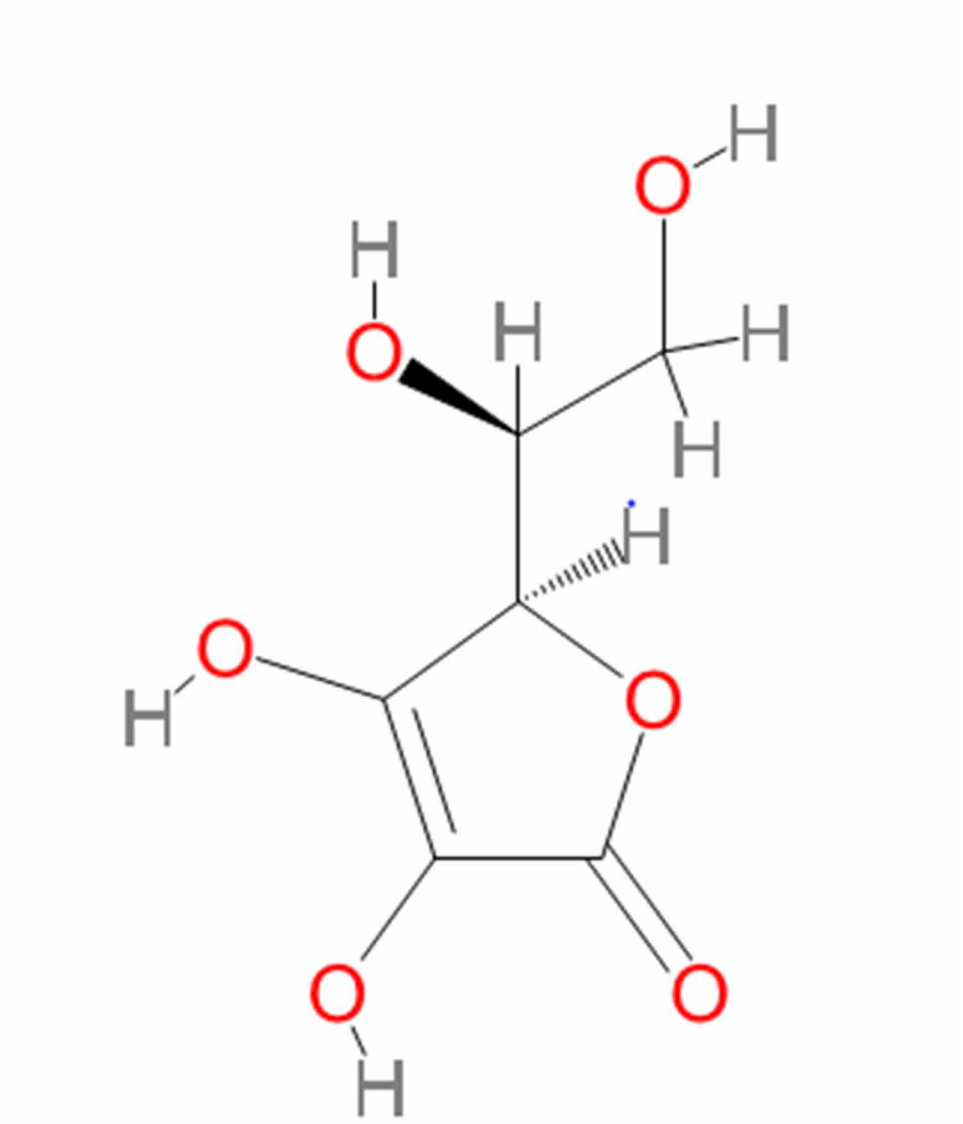
Cardiac Glycosides

These are the compounds which are not good for human health as they are poisonous and sometimes show lethal effects. Though, they are harmful, still they are used as therapeutic agents for heart diseases (Harborne, 1973). At the times of heart failure, the drugs derived from this has been utilized which interferes physiology of the heart. In congestive heart failure, it has been seen that the heart doesn't able to pump the blood properly as a result of which it builds up in the pulmonary area (Ogunwenmo *et al.,* 2007; Ngoci *et al.,* 2011).

BIOACTIVE MOLECULES IN DIFFERENT PLANTS AND THEIR THERAPEUTIC USE

There are various plant species which have been used as therapeutic agents. The Aescin bioactive molecule has been derived from the plant *Aesculus hippocastanum* L. which is used to treat inflammatory diseases (Sirtori, 2001). The other bioactive molecule of plant *Allium sativum* L. i.e., allicin used to lower the lipid concentration in the body as well as also acts against the bacterial diseases (Jain *et al.,* 1993). The bioactive molecule andrographolide derived from the *Andrographis paniculata* L. known to protect the lever and used for curing liver related problems (Kapil *et al.,* 1993). In the treatment of malaria, drugs derived from the bioactive molecules artemesinin obtained from the plant *Artemesia annua* L. have been used (Lin *et al.,* 1987). The berberine molecule of *Berberis vulgaris* L. is used to treat bacterial diseases and diarrhea (Amin et al., 1969). Rheumatoid arthritis drugs comprises of bioactive molecules boswellic acid of *Boswellia serrata* L. (Safayhi *et al.,* 1992; Taneja & Dhar, 1996). A Saikosaponin D molecule (plant *Bupleurum Chinese* L.) is known to increase the efficiency of liver metabolism (Yen *et al.,* 1991). The capsaicin molecule of *Capsicum annuum* L. used as topical analgesic (Bernstein et al., 1987). The emetine (*Cephaelis ipecacuanha* L.) molecules act as antiamebic in dysentery (Botero, 1978). Quinine is the compound extracted from the *Cinchona succirubra* L. plant and the molecule exploited for treating malaria (Leung, 1980). The serious diseases like Gout, Hepatitis and cancer found to be treated with the bioactive molecule of plant *Colchicum autumnale* L. known as colchicines (Lange *et al.,* 2001; Warnes, 1991). Curcumin molecule of *Curcuma longa* L. used to treat bacterial diseases as well as also works against tumor (Nagabhushan & Bhide, 1992). The challenging conditions in which failure of the heart has to be treated, the drug derived from the plant *Digitalis orientalis* L. molecule digoxin is used (Foss and Benezra, 1980; Campbell & MacDonald, 2003). The severe effects of migraine have been treated with drugs derived from ergotamine and this is also used at the time of child birth (Kreilgard, 1977). To maintain the hemostasis of the body, hydrastine (*Hydrastic Canadensis* L.) is prescribed (Genest, 1969). Most of the pain killers consist of aspirin as one of the components and this is the bioactive molecule of *Salix alba* L. (Kaul *et al.,* 1999). One of the compound synthesize from *Silybum marianum* L. i.e., silybin is utilized as a protective agent of the liver (Hobbs, 1992; Wellington and Jarvis, 2001). Besides this, the other fascinating properties of this compound make it more consumable including its

Figure 1. Vitamin C



antioxidant properties. The warts which occur on the skin induced by the virus population can be treated with podophyllotoxin (*Podophyllum peltatum* L.) molecules. It is also used to inhibit the uncontrollable growth of cancerous cells (Jardine, 1980; Canel *et al.,* 2000). Vinblastine is mostly used in chemotherapy for controlling the growth of tumor cells. This molecule is extracted from the plant *Vinca rosea* L. (Van der *et al.,* 2004). Another molecule which is consumed by the diabetic patient is as sweet as sugar without its harmful effects. This sweetener has been prepared from the natural active compound stevioside

present in the *Stevia rebaundiana* L. (Yamamoto *et al.,* 1985). The strychnine (*Strychnosnux vomica* L.) molecule is a potent stimulator of central nervous system (Muhtadi, 1986).

Figure 2. Vitamin E

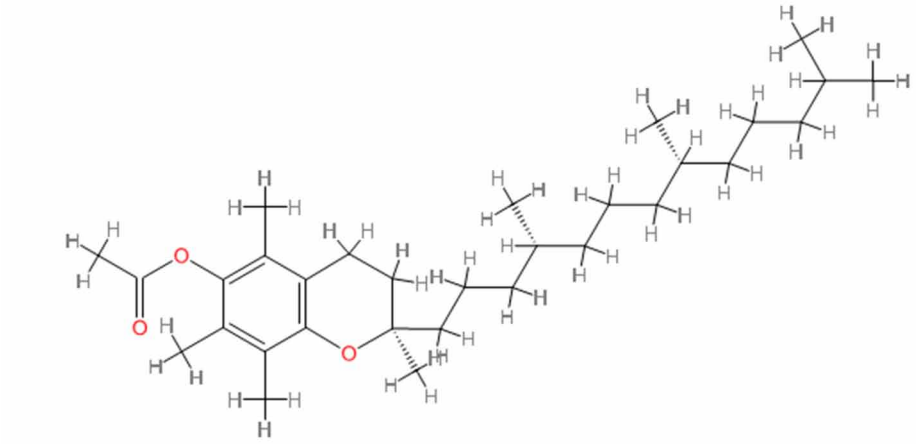


Figure 3. Saponin

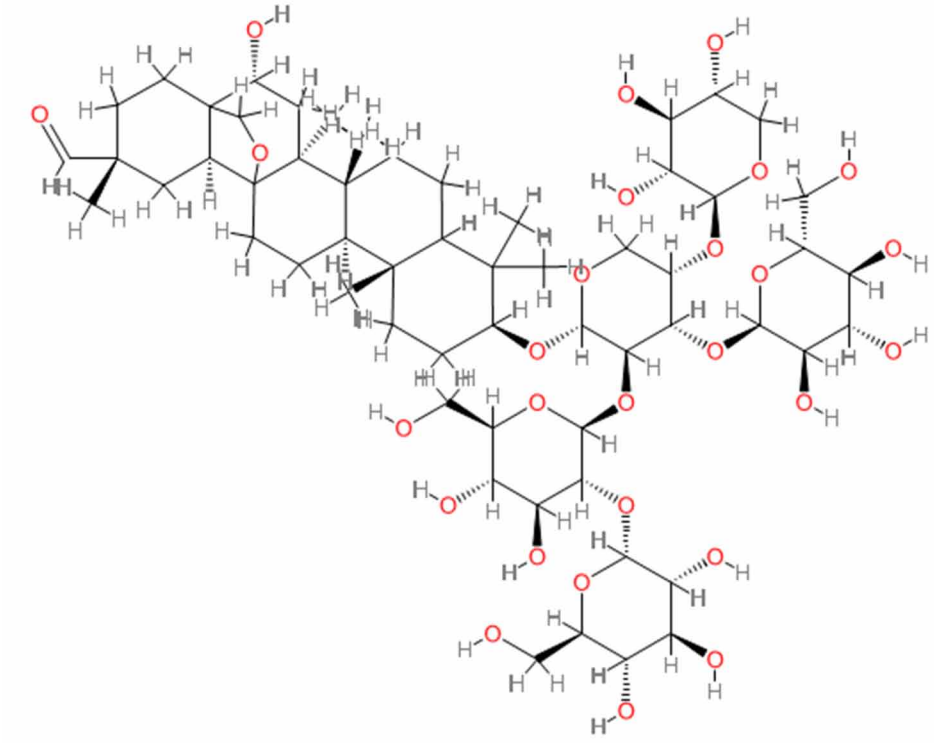
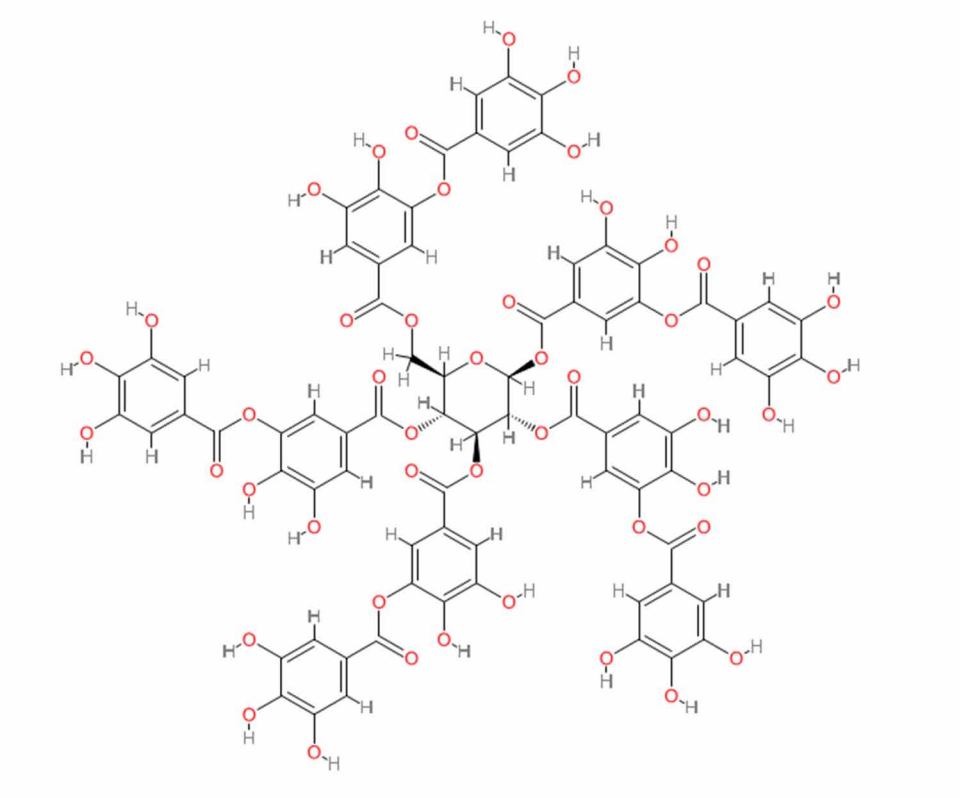


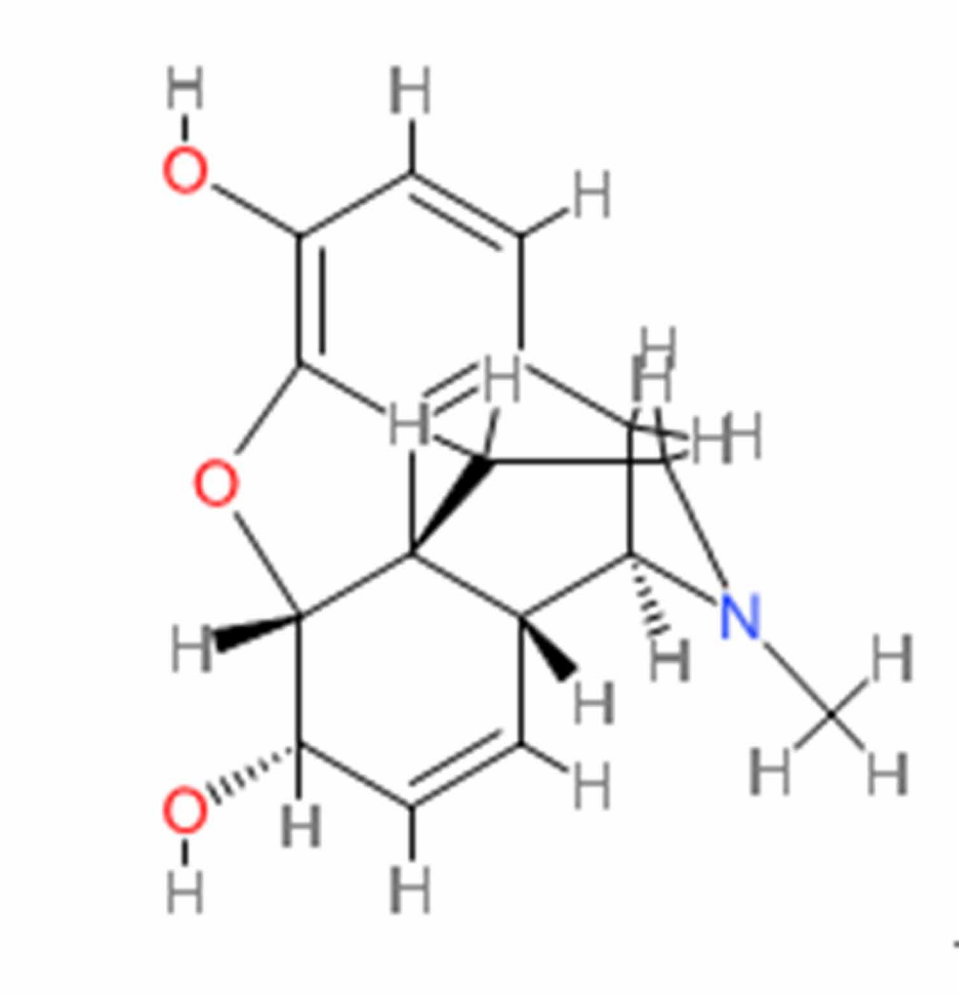
Figure 4. Tannic Acid (Tannin)



There are some bioactive molecule whose uses in treating diseases have been known from ancient times, but now-a-days, their range have been extended for treating other diseases. The bioactive molecule rohitukine present in *Dysoxylum binectarifarum* L. traditionally used to treat rheumatic disease, however, its characteristics presently exploited for the treating the cancer (Wang, 2000). Likewise, the rutin compound (*Eucalyptus macrorhyncha* L.) previously used as insect repellant but its utilization as drugs for treating the fragileness of capillaries is commendable (Levitan, 1951). The compound gingkolide A has been exploited for asthma and in present conditions it has been consumed as drug for increasing the memory which is mostly useful for Alzheimer's patient (LeBars *et al.,* 1997). The plant bioactive molecule (hypericin) utilized to combat against depression. Now, it has been used to cure viral diseases (Gulick, 1999). Though, picroside (*Picrorhiza kurroa* L.) recommended in fever and dyspepsia but it can be consumed as protective agent of liver (Vaidya et al., 1996). The sanguinarin extracted from *Sanguinaria canadensis* L. traditionally consumed by the people for improving the skin and to purify their bloods. Besides this, it has been recommended for curing the gum diseases and controlling plaque (Shamma, 1972). From *Taxus baccata* L., taxol drug has been isolated and prepared which is utilized in curing spasms and rheumatid disease problems. But now-a-days, it is used in chemotherapy of patients (Legha, 1990; Suffness, 1995).

Some of the bioactive molecules have been identified newly from various plants possessing therapeutic uses. For example, khellin extracted from the plant *Ammi visnaga* L. is a potent vasodilator (Ubeda & Villar, 1989). Similarly, the *Aristolochia indica* L. (Aristolochic acid) used to treat the fertility issues

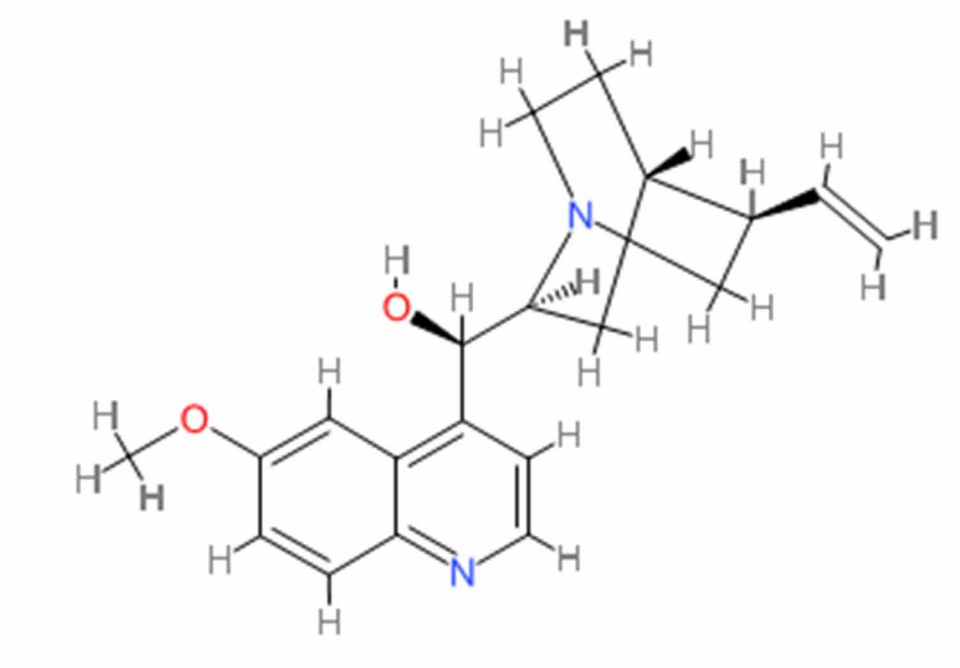
Figure 5. Morphine (Alkaloid)



(Mathur *et al.,* 1980). Naringenin (*Citrus paradisi*) prescribed for the persons suffering from bacterial infections and cancer (Ameer *et al.,* 1996). Hesperidine (*Citrus sinensis* L.) has been consumed by the diabetic patients and it is used for curing viral disease (Garg *et al.,* 2001). Forskolin (*Coleus forskolii* L.) also used as therapeutic agent in blood pressure related problems as well as in spasm treatment (Ammon & Mueller, 1985; De Souza *et al.,* 1983). The plant of *Betula alba* possessed betulinic acid which is effective in the treatment of AIDS and act as tumor suppressor agent (Cichewicz & Kouzi, 2004). Camptothecin derived from the plant *Camptotheca acuminata* L. showed impressive activity against the tumor cells by inhibiting their growth (Wall & Wani, 1980). The skeletal muscle of the body can be relaxed at the time of disease by using the drug cissampareine (*Cissampelos pareira* L.) (Kupchan *et al.,* 1965). The bioactive molecules shikonin, ellipticine, lycopene and lapachol used in the treatment of cancer which has been derived from *Lithspermum erythrorhizon* L., *Ochrosia elliptica* L., *Lycoperscion esculentum* L. and *Tabebuia avenallanedae* L., respectively (Block *et al.,* 1974; Paoletti *et al.,* 1980; Rao *et al.,* 1998; Chen *et al.,* 2003; Garbett & Graves, 2004). Lycopene, cynarin, resveratrol and carnosol drug possesses antioxidant activities and these compounds extracted from the following plants: *Lycoperscion*

esculentum L., *Cynara* scolymu L., *Polygonum cuspldatum* L. and *Rosmarinus officianalis* L. (Aruoma *et al.,* 1992; Gebhardt, 1997; Rao *et al.,* 1998; Bhat *et al.,* 2001).

Figure 6. Quinine (Alkaloid)



COMMON PLANT-BASED NATURAL BIOACTIVE MOLECULES

Resveratrol

Among all the bioactive molecules, this is one of the molecules which are present in grapes and other plants also possessing the antioxidant properties (Mukherjee *et al.,* 2010). They act as antioxidants by inhibiting the production of ROS and RNS in the body and enhance the metabolic pathways which help in the reduction of harmful radicals. Besides this, they also have the anti-inflammatory properties (Lastra & Villegas, 2005). They also involved in the repairing of DNA, anti-aging, regulating cell cycle and other various activities by NAD-dependent protein deacetylases regulation (Borra *et al.,* 2005). In females, it plays important role as it prevents the bone from losing their bone density due to the increasing age (Baxter, 2008).

Epigallo-Catechin-3-Gallate

Green tea has gained popularity due to its antioxidant properties. Though, they decrease the production of free radicals which cause damage to the cells but also involved in the prevention of inflammatory processes in the cell. The bioactive molecule Epigallo-Catechin-3-Gallateextracted from the leaves also

Table 1. Role of Bioactive molecules in treatment of major Chronic Diseases

Diseases	Bioactive Molecules	Uses	References
Diabetes	Polyphenols Carotenes Vitamins C Vitamin E	Antioxidant	Kiec-Wilk & Mykka, (2008)
	Cinnamaldehyde Epigallocatechin Chlorogenic acid	Reducing Hypoglycemic effect, protect the inhibition of amylase and increasing insulin efficiency	He *et al.,* (2006); Zhu *et al.,* (2017); Meng *et al.,* (2013)
	Lycopene Zeaxanthin Carotene β-cryptoxanthin	Prevent type II diabetes mellitus	Coyne *et al.,* (2005)
Cancer	Curcumin	Preventing the formation of tumor	Dhillon *et al.,* (2008); Bayet-Robert *et al.,* (2010)
	Lycopene	Cell growth inhibitor	Kucuk *et al.,* (2002)
Neurodegenerative Diseases	6-Shogaol	Reduces the production of IL-1β, prostaglandin E2, and TNF-α	Ha *et al.,* (2012)
	Ginkgolide B	Decreases the NF-κβ and increasing Bcl2	Gu *et al.,* (2012)
	Quercetin	Anti-oxidant, antiviral	Li *et al.,* (2016)
CVD	Resveratrol	Enhance inflammation	Tomé-Carneiro *et al.,* (2013)
	Lycopene	Reducing bad cholesterol level, antioxidant	Hadley *et al.,* (2003); Bohn *et al.,* (2013); Story *et al.,* (2010)
	Vitamin C	Reducing bad cholesterol level, antioxidant	Chambial *et al.,* (2013)
	Vitamin E	Inhibiting or decreases the lipid peroxidation	Saremi & Arora, (2010)
	Omega 3 Fatty Acids	Reduces BP levels	Jain *et al.,* (2015)

*CVD= Cardiovascular Diseases, BP=Blood Pressure

protects the heart related diseases and works against the diseases caused by virus (Chacko *et al.,* 2010; Singh *et al.,* 2011).

There are several DNA methyltransferase enzymes which targets the Cytosine-phosphate-Guanine rich areas by introducing methyl groups to them which sometimes acts as transcriptional inhibitors or inducers depending on the amino acid which gets methylated (Singh et al., 2011). However, these enzymes are also involved in the aging process. The bioactive molecule Epigallo-Catechin-3-Gallate works against this and limits the expression of these enzymes and act as anti-aging agent. It has been known that DNA methylation in the cells sometimes lead to tumor formation in the body as some of the anti-tumor gene gets suppressed. This molecule also prevents the tumorigenesis by restricting this enzyme. Another enzyme i.e., Glutathione-S-transferase are known to remove the drugs from the body. This enzyme expression increases in the presence of this bioactive molecule (Yang *et al.,* 2010).

Curcumin

This is one of the bioactive molecules present in the turmeric plant which has a long history in curing diseases. The importance of the turmeric in the ancient medicinal system of India provides the diseases which can be cured from this. In India, it has been used in cooking any meal along with other spices. It is evident from the recent studies that it provides protection against various diseases (Gupta *et al.,* 2013). They also inhibit the inflammation and also act as anti-tumor agent (Hatcher *et al.,* 2008).

Lycopene

This is the active compound of tomato plant which provides its characteristics color red to the plant (Story *et al.,* 2010). It is evident from various studies that it increases the level of good cholesterol in body and decreases the bad cholesterol levels. It also possesses antioxidant activity (Hadley *et al.,* 2003; Story *et al.,* 2010; Bohn *et al.,* 2013). One of the studies claimed that consumption of lycopene on a daily basis improved the condition of cardiovascular diseases (Gajendragadkar *et al.,* 2014).

Ascorbic Acid (Vitamin C)

Vitamins constitute the micronutrient part in the body whose small quantity has been required in the body. Most of the vitamins have been consumed from the dietary sources such as lemon, orange and various other fruits and vegetables having the citric acid content is high consists of Vitamin C (Chambial *et al.,* 2013). They have great antioxidant activity which helps in increasing the metabolic rates as well as protect the heart from various diseases (Chambial *et al.,* 2013).

Omega 3 Fatty Acids

This is one of the classes of fatty acids which is found in plants and animals both (Tur *et al.,* 2012). They possess the ability to bind to the membranes of the body along with that they decrease the inflammation in the body by reducing the cytokine production (Swanson *et al.,* 2012). They are used for maintaining the B.P. along with decrease in the triglyceride levels and they regulate various metabolic pathways (Jain *et al.,* 2015).

CONCLUSION

It has been seen that bioactive molecules extracted from either medicinal plants or normal plants act as therapeutic agents in various diseases. Most of the phytochemicals or bioactive molecules have been known traditionally, however, their utilization in other diseases extended. The intake of these molecules either directly or indirectly confers various health benefits. The benefits provided by them such as providing protection against various diseases caused by the microorganisms, CVD, increasing the metabolic activity, reducing inflammatory activity etc. makes them consumable on a daily basis. Though, they are known to provide benefits to the human health, still, it have been less known about their mechanism. Recent studies points out towards the basic pathways of metabolism which have been affected from their consumption. Such as the inflammation pathway which includes cytokine, the pathway of lipid metabolism

which reduces the level of bad cholesterol and decreasing the risk of heart diseases, reducing the production of free radicals etc. They are the part of diet traditionally and now; they are important constituent of medicines. The bioactive molecules which have been extracted from the higher plants proven to be more successful as therapeutic agents in comparison to those extracted from another organism. Though, they are very beneficial for the human health, still, their mixtures with other molecules are still challenging as their reaction with other compounds could be either harmful or beneficial.

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Chapter 2
Decoction and Their Biological Activities

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ABSTRACT

Modern procedures and unique approaches to therapeutic modification get a boost from ethnic expertise. Ayurvedic medicine is a specialized form of traditional medicine that developed in India and the surrounding subcontinents. Decoction is a basic Ayurvedic dose form that is one of the most commonly used and thought to be one of the most effective in traditional medicine. Plant ingredients are chopped into small pieces and soaked in a certain amount of water in an earthenware pot and other vessels to make decoctions. Polyherbal formulations, such as decoctions, have long been used in Ayurveda to treat a variety of ailments. It has been discovered that decoction can aid in the treatment and prevention of a variety of diseases, including neurodegenerative diseases, nasal diseases, allergic rhinitis, cancer, jaundice, liver disorders and metabolic diseases, cold pathogenic diseases, non-alcoholic fatty liver disease, and so on. This chapter delves into one of the oldest types of extractions utilized by our forefathers to treat a variety of ailments.

INTRODUCTION:

Traditional practices in modern lifestyles are currently emerging on a daily basis. Ethnic knowledge provides wings to modern methodologies and novel approaches to therapeutic modification. In addition, numerous older processes for preparing dosage forms are still in use. Various current and traditional

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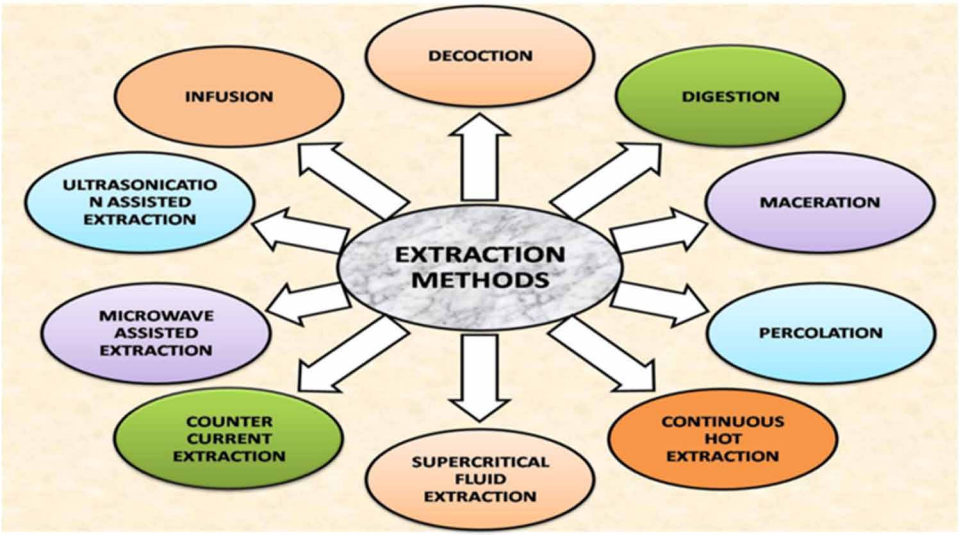
methods are utilized to extract active components. Extraction is one of the processes of separating active components of plant or animal tissues from their inert counterparts using certain solvents. Aside from the well-established traditional extraction procedures, some of which are still widely used today, for the extraction of the active components of medicinal plants and expression, the main techniques are digestion, infusion, percolation, decoction, aqueous alcoholic extraction by countercurrent extraction (CCE) and fermentation, cold fat extraction like enfleurage, cohobation and protoplast extraction (Sasidharan *et al.,* 2011; Zhang *et al.,* 2018 & Manousi*et al.,* 2019). Some of the extraction techniques were mentioned in Fig 1. This chapter deals with one of the oldest form of extractions used by our ancestors to cure various health problems. Decoction is a process of extracting water-soluble and thermostable components. Decoctions are made by cutting plant materials into little pieces, soaking and boiling them in a specific amount of water in an earthenware pots and in different containers (Manousi*et al.,* 2019 & Nafiu*et al.,* 2017).The extraction of thermolabile or volatile components is not possible using decoction (Zhang *et al.,* 2018).

Figure 1. Different Methods of Extraction



Various forms of Phytochemicals Decoctions:

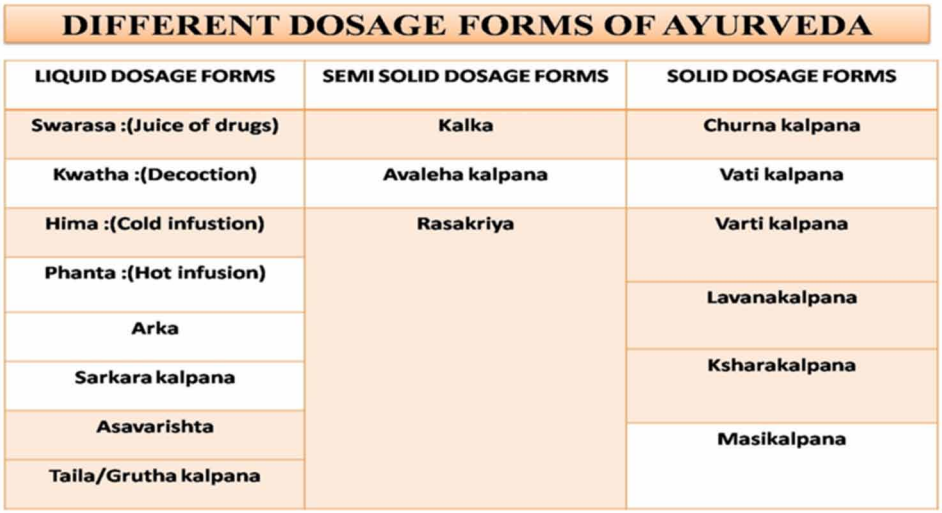
Strong Decoction: Strong decoctions are produced in two methods, depending on the type of plant material employed. The first method includes boiling the mixture for a longer period of time. When working with a larger portion of hardwood bark, longer boiling times, up to 2 hours or more. Similarly, the second, when tiny wooden parts are boiled for 20 minutes, they are left to soak overnight before being strained (Nafiu *et al.,* 2017).

Dried Decoction: The dried decoctions are made by a decoction of the herb formulations in big batches (in huge tanks) and then emptying the fluid from the residues. The fluid is then evaporated (by vacuum and heat) to make syrup. To make the powder, the syrup is placed into a spray dryer with a powder carrier (Nafiu *et al.,* 2017).

Ayurvedic system of Medicines:

Ayurvedic medicine is a customized system of traditional medicine that originated in India and the neighboring subcontinents. It is a life science that takes a holistic approach to health and provides tailored medicine (Farooqui *et al.,* 2018 & Chauhan *et al.,* 2015). World Health Organization report says, approximately 70–80% of the world's population relies on complementary and alternative treatments. While Ayurvedic medicine is extremely efficient, the proper mechanism of action, pharmacology, pharmacokinetics and pharmacovigilance profile of significant Ayurvedic pharmaceuticals are still unknown. Additionally, thorough knowledge of Ayurveda's fundamental principles is not widely acknowledged scientifically due to a dearth of evidence. They obtain the majority of their healthcare from herbal sources. Ayurveda contains a detailed account of numerous dose forms that dates back over 5000 years. (Arun. *et al.,* 2014 & Chauhan *et al.,* 2015). Various dosage forms were used in Ayurveda and are categorized into three major forms as per their physical status (fig no. 2).

Figure 2. Different types of Ayurvedic dosage forms

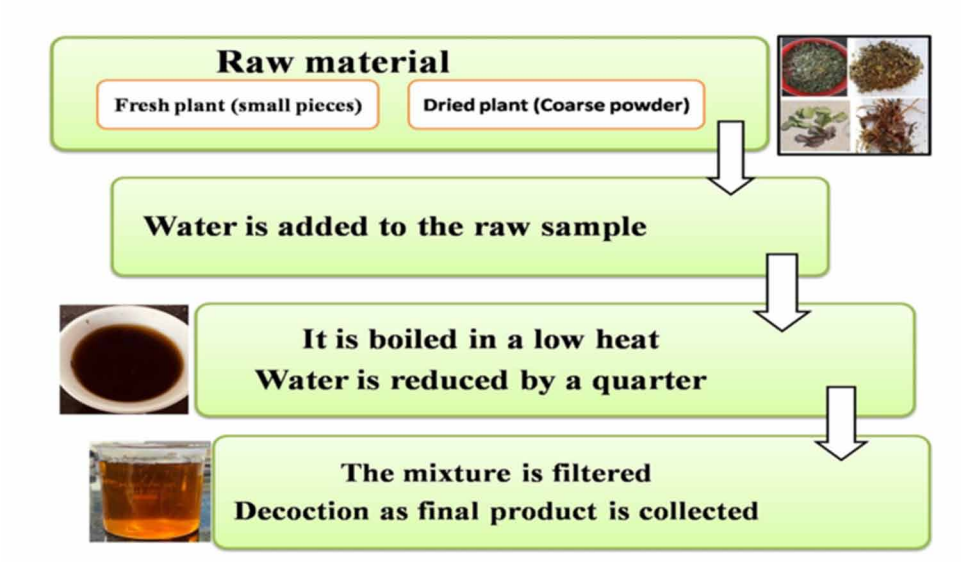


Decoction is a fundamental Ayurvedic dosage form, that is one of the most regularly used and believed to be one of the most effective dosage forms in traditional medicines (Dahanayake*et al.,*2019&Tacchini*et al.,*2015).In Ayurveda decoction is one of the liquid dosage forms called as (*Kwatha*) (Arun *et al.,*2014). A basic procedure for the preparation of decoction is explained in (fig 3).

Decoctions in the Management of Various Problems:

Polyherbal compositions like decoctions have also been utilized for a long time in Ayurveda to treat variety of illnesses. Herbal medication can aid in the treatment of disorders such as cancer, liver troubles, nasal and allergy problems, respiratory tract infections and pathogenic infections (Bhatt and Deshpande 2020). Systematic decoction is based on specific medical concepts and it is an approach to living a healthy

Figure 3. A simple approach for making a decoction



lifestyle that is consistent with accepted views about the prevention of disease and the promotion of health that have been around for a while (Ahmad et al., 2021). The availability of conventional medications with effective therapeutic potential derived from natural sources, as well as valuable historical treatment experience, give a more prominent therapeutic strategy against COVID-19. Traditional Chinese medicine (TCM) has extensive experience in the long-term prevention and treatment of epidemics and is characterized by broad-spectrum immunity, universal adaptability and foresight. TCM's distinct advantages have drawn increasing attention to the epidemic prevention and treatment of COVID-19 (Yang et al., 2020; Ren et al., 2021).In light of the current circumstances, several treatment modalities have been carefully considered, including traditional medicine, which has been widely employed during previous epidemic outbreaks, such as SARS and H1N1 influenza and is expected to be largely used in the future (Luo et al., 2020). Up to this point, only three nations have produced guidance on traditional regimens for the prevention and management of COVID-19, including India, China and the Republic of South Korea (Ang et al., 2020).Some of them are discussed in Table 1.

CONCLUSION:

At this time, consumers are finding it increasingly difficult to buy health insurance because of escalating health care costs. Medications based on drugs are both prohibitively expensive in developing nations like India and troublesome in the West due to the numerous adverse effects. In Ayurvedic medicine, preparations like Decoction can help to prevent disease from developing. Decoctions appeared to be more effective against cancer cell lines, infections and germs in several investigations.

Table 1. Various decoctions role in the management of different diseases

Treatment for		Decoction used	Components involved	References
Neurodegenerative diseases		Danggui-shaoyao-san decoction	*Paeoniae Radix Alba, Angelica Sinensis Radix, Chuanxiong Rhizoma, Poria, Atractylodis Macrocephalae Rhizoma and Alismatis Rhizoma.*	Luo *et al.,* 2016
Nasal diseases and Allergic rhinitis		Tamalakyadi decoction	*Phyllanthus niruri L., Terminalia chebula Retz., Premna herbacea Roxb., Piper retrofractum Vahl., Piper longum L., Solanum trilobatum L., Tinospora cordifolia (Tunb.) Miers, Zingiber ofcinale Roscoe, Piper nigrum L., Solanum melongena L., Solanum xanthocarpum L., Justicia adhatoda L.*	Dahanayake *et al.,* 2019
Cancer		Merwilla decoction	*Merwilla plumbea (Lindl.) Speta*	Koduru *et al.,* 2007
		Scilla decoction	*Scilla natalensis Planch.*	
		Eucomis decoction	*Eucomis autumnalis (Mill.)*	
		Pittosporum decoction	*Pittosporum viridiflorum Si*	
		Curtisia decoction	*Curtisia dentata (Burm.f.)*	
	Internal and external cancer	Sutherlandia decoction	*Sutherlandia frutescens L. R*	
	Colorectal cancer	Shaoyao Decoction	*Paeonia lactiflora,Angelica sinensis,Coptis chinensis,Areca catechu,Aucklandia lappa,Glycyrrhiza uralensis,Rheum officinale,Scutellaria baicalensis, and Cinnamomum tamala*	Wang et al., 2019
	Cervical cancer	Guizhi-Fuling-decoction	*Cinnamomum cassia, Paeonia lactiflora, Paeonia suffruticosa, Prunus persica and Poria cocos*	Zhang & Zhang, 2008
	Gastric cancer	Banxia Xiexin Decoction	*Pinellia ternata, Scutellaria baicalensis, ginseng, dried ginger, licorice, Chinese-dates, and Coptis chinensis*	Sun *et al.,* 2021
	Lung cancer	Haimufang decoction	*Sargassum, Ostreae Concha, Menispermi Rhizome and Solani Nigri Herba*	Ma *et al.,* 2020
Coronavirus Disease		Maxing Shigan decoction	*Ephedra sinica, Semen armeniacae amarum, Gypsum Fibrosum and Glycyrrhiza uralensis*	Li *et al.,* 2021
		Qingfei Paidu Decoction and Ma Xing Shi Gan Decoction	*21 herbs mainly Herba Ephedrae, Radix Glycyrrhizae, Semen armeniacae amarum, Gypsum fibrosum, Ramulus Cinmomi, Rhizoma Alismatis and Polyporus umbellatus*	Yang *et al.,* 2020
		He-Jie-Shen-Shi decoction	*Bupleurum chinense*, *Scutellaria baicalensis* Georgi, *Pinellia ternata*, *Glycyrrhiza uralensis*, *Codonopsis pilosula*, *Poria cocos*, *Alisma plantago-aquatica subsp. orientale*, *Atractylodes macrocephala*, *Neolitsea cassia*, *Coix lacryma-jobi var. ma-yuen*, *Pyrrosia lingua*, *Plantago asiatica* and *Benincasa hispida*	Hu *et al.,* 2021
Jaundice, liver disorders and various metabolic diseases		Yinchenhao decoction	*Artemisiae scopariae herba, Radix et Rhizoma Rhei and Gardeniae Fructus.*	Huang *et al.,* 2017
Cold Pathogenic Diseases		Mahuang Decoction (Ephedra Decoction)	*Herba Ephedrae, Ramulus Cinnamomi, Semen Armeniacae Amarum, and Radix Glycyrrhizae*	Yao *et al.,* 2013
Coronary heart disease, blood stasis syndrome		Buyang Huanwu decoction	*Milkvetch Root, Chinese Angelica, Szechwan Lovage Rhizome, Red Peony Root, Earth Worm, Peach Seed and Safflower*	Hui *et al.,* 2010
Non-alcoholic fatty liver disease		Lingguizhugan decoction	*Poria, Ramulus Cinnamomi, Rhizoma Atractylodis Macrocephalae, and Radix Glycyrrhizae*	Xu *et al.,* 2020
Respiratory tract infection, nosocomial pneumonia, chronic Bronchitis, perennial allergic rhinitis, idiopathic sweating and augment appetite in end-stage cancer patients, severe acute respiratory syndrome, asthma, hepatic-fibrosis, pulmonary- fibrosis and dermatitis		Yu Ping Feng decoction	*Astragali Radix, Atractylodis Macrocephalae Rhizoma and Saposhnikoviae Radix*	Zuo *et al.,* 2018
Damp-heat jaundice and other hepatic diseases		Yīn-Chén-Hāo decoction	*Artemisia capillaries, Gardenia jasminoides and Rheum rhabarbarum*	Li *et al.,* 2017
Inflammation of upper respiratory tract		Joshanda	*Althaea officinalis*, *Cordia latifolia*, *Glycyrrhiza glabra, Malva sylvestris, Onosma bracteatum Viola odorata* and *Zizyphus Sativa*.	Abdullah *et al.,* 2015
COVID-19		AYUSH kwath	*Ocimum sanctum* L., *Cinnamomum verum* J. Presl., *Zingiber officinale* Roscoe and *Piper nigrum* L.	Ahmad *et al.,* 2021
Acute infectious diarrhoea		Guava leaf decoction	*Leaves of Psidium guajava*	Birdi *et al.,* 2020
Hemorrhoidal disease		Liang-Xue-Di-Huang Decoction	*Sophora japonica* L., *Platycladus orientalis* (L.)Franco, *Sanguisorba officinalis* L., *Coptis chinensis* Franch., *Rehmannia glutinosa* Libosch, *Angelica sinensis*(oliv) Diels, *Citrus aurantium* L., *Scutellaria baicalensis* Georgi, *Paeonia lactiflora* Pall., *Schizonepeta tenuifolin* Briq., *Trichosanthes Kirilowii* Maxim, *Cimicifuga heraclei* folia. Kom and *Glycyrrhiza uralensis* Fisch.	Shi *et al.,* 2020
Immune and Neuroendocrine systems.		Liuwei Dihuang decoction	Radix Rehmanniae, Dioscorea opposite, Cornus officinalis, Paeonia suffruticosa, Alisma plantago-aquatica and Poria cocos	Zhou *et al.,* 2016
Anti-diabetic		ShengMai-Yin and Ganmaidazao decoction	Radix Ginseng, Radix Ophiopogonis, Fructus Schisandrae, Fructus Tritici levis and Fructus Zizyphi Jujubae	Li *et al.,* 2019
Antidiarrheal and Antioxidant		*Matricaria recutita* L. Decoction	Chamomile plant	Sebai *et al.,* 2014
Cancer and Antimicrobial		Decoctions of *Castanea sativa* flowers	Chestnuts plant	Carocho *et al.,* 2014
Anti-obesity		Varanadi kashayam (decoction)	*Crataeva religiosa, Strobilanthes ciliatus, Asparagus racemosus, Plumbago zeylanica, Chenomorpha fragrans, Aegle marmelos, Aristolochia bracteolate, Solanum melongena, Aerua lanata, Pongamia glabra, Holoptelia integrifolia, Premna corymbosa, Terminalia chebula, Moringa olifera, Desmostachya bipinnata* and *Semicarpus anacardium.*	Chinchu *et al.,* 2020
Antihypertensive Activity		San Cao Decoction	*Prunella vulgaris* L., *Glycyrrhiza uralensis* Fisch, *Glycyrrhiza inflata* Bat., *Glycyrrhiza glabra* L., *Paeonia lactiflora* Pall, *Leonurus japonicus* Houtt and *Gentiana lutea* L	Ma *et al.,* 2019
Antibacterial, antimalarial, anti-diarrheal and anti-leshimania		Echinops kebericho Decoction	Echinops kebericho herb	Deyno *et al.,* 2020
Chronic prostatitis/chronic pelvic pain syndrome		Qian-Yu decoction	*Radix astragali, Herba epimedii, Herba leonuri, Cortex phellodendri and Radix achyranthis bidentatae*	Zhang *et al.,* 2017
AChE inhibition activity and antioxidant potential		*Santolina impressa* Decoction	*Santolina impressa* leaves, stems and capitula	Rodrigues *et al.,* 2020

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Chapter 3
Role of Medicinal Plants and Herbs in Veterinary Medicine

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ABSTRACT

Ethnoveterinary medicine is a branch of ethnobotany concerned with the study of traditional remedies. Ethnoveterinary methods are as old as domestication of numerous livestock species when it comes to animal healthcare. Herbal medicine has experienced a variety of conceptual modifications over time, yet its tone has stayed mostly same from antiquity to the present. Antibacterial, antifungal, insecticidal, and antioxidant action has been demonstrated for plants. Herbal treatment strives to not only cure the underlying cause of the illness, but also to reverse aberrant symptoms and restore the animals' health and vigour.

INTRODUCTION

Medicinal plants have been used as a source of healing in local communities all over the world for thousands of years. Nonetheless, for around 85 % of the world's population, it is still significant as a primary healthcare technique, and as a drug discovery resource, with 80% of all synthetic medicines derived from them (Bauer & Brönstrup, 2014; Singh & Navneet, 2016, 2017a).It is unsurprising that people have utilised the same plant remedies for the animals in their care for as long as humans have been

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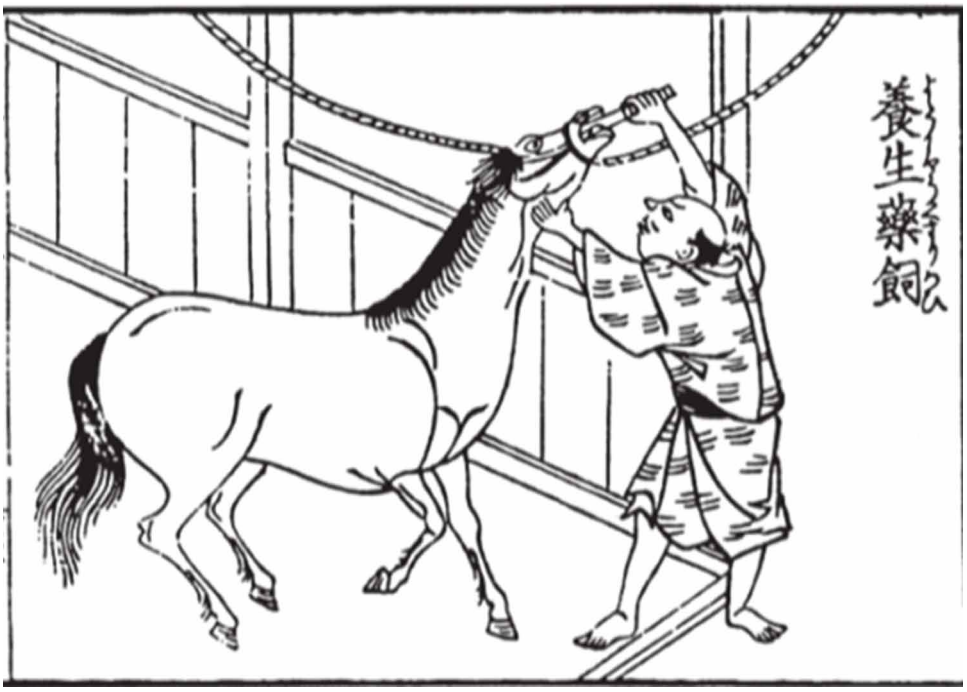
Figure 1. Administering liquid medicine with a bamboo bottle is an aspect of the old Chinese-Japanese art of horse healing.



linked with animals. Thus, for most of history, the evolution of veterinary botanical medicine, the earliest kind of veterinary medicine, has paralleled the progress of human medicine. Indeed, herbal medicine has experienced a lot of conceptual transformations throughout history, but its tone has remained substantially unaltered from antiquity to the present. Herbal medicine is holistic, empiricist, and vitalist in attitude, and some herbalists believe that it should stay such even while contemporary medicine attempts to embrace the use of herbs as "drugs" in search of the "active ingredient." This "scientism," which may verge on reductionism, is essentially a new philosophy in the context of herbal medicine (Pešić, 2015).

Evidence shows that Ayurveda, which originated in India, was possibly the first medicinal system. The use of medicinal herbs in the treatment of people and animals is mentioned in the Rig Veda, the earliest source of human knowledge, written between 4500 and 1600 BCE. The "Nakul Samhita," published about the same time, was possibly the first book on the use of herbs in the healing of animals. Animal husbandry chapters such as "Management and Feeding" may be found in ancient texts such as the Skandh Puran, Devi Puran, Harit, and others. Palkapya (1000 BC) and Shalihotra (2350 BC) were well-known veterinarians who specialised in elephant and horse care (Unknown, 2004). King Asoka (274-236 BC) commissioned individuals to cultivate herbs for use in the care of ill and elderly animals (Wynn & Fougère, 2006). Ricinius, pepper, lily, and valerian are among the medicines described in early Ayuvedic literature of the CharakaSamhita (200 BC-AD 200). Vasant Lad characterises the foundation of Ayurveda ("life science") in a way that mirrors the Tao of Chinese medicine and the humours of Greek medicine:

In 3700 BC, a Chinese monarch called Shen Nong composed one of the earliest known and longest surviving Materia Medica. Shen Nong (the Divine Farmer) is regarded as the legendary founder of

Chinese herbal medicine. Hundreds of plants are said to have been tasted by him, identifying those that may be used as cures, and characterising their qualities. As a result of his work, several plants are now commonly utilised in treatment, and information has been passed down through oral tradition for generations. His herbal Materia Medica book included herbal Materia Medica for both humans and animals. It's worth noting that it talked about the antifever effects of Artemesia annua (Chinese wormwood), which has recently been proved to be particularly efficient against malaria (Yang, 1997).

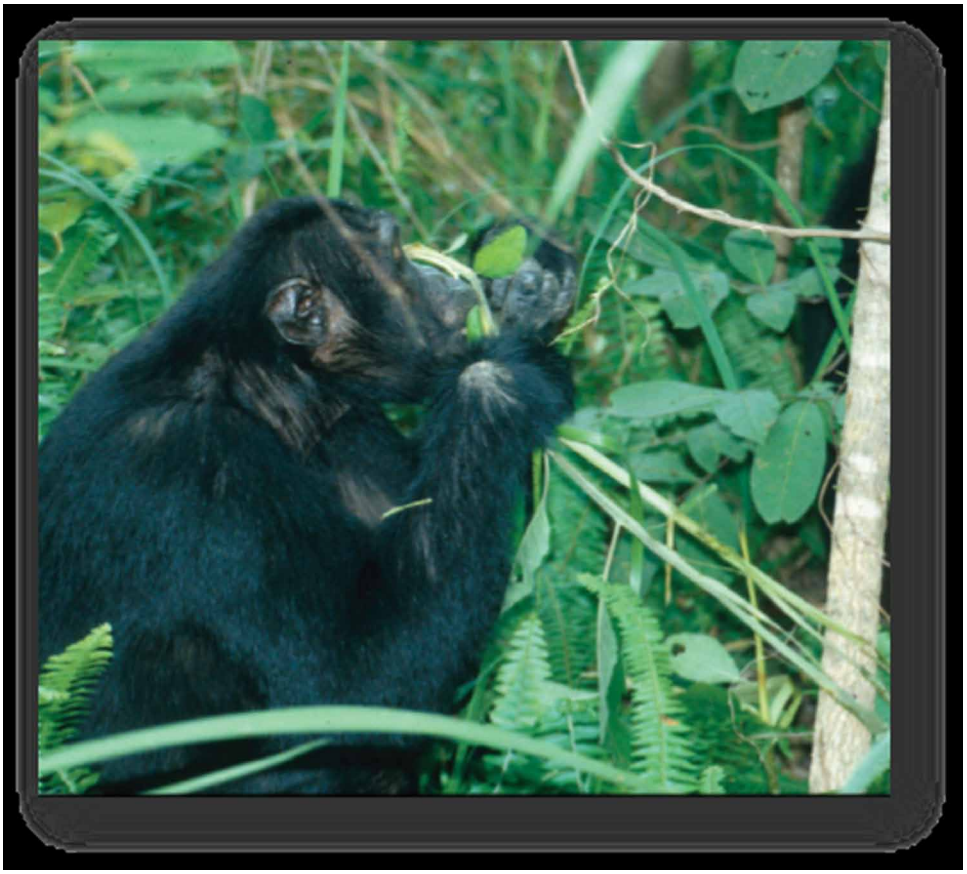
When compared to the Egyptians, the ancient Greek and Roman societies advanced veterinary science in comparable but slightly distinct paths. The "Hippiatrika" is one of the first writings we come across that mentions Roman practitioners and their study of horses (Walker, 1991). Around 500 BC, the name "Hippiatros" was used in Greece to designate to horse physicians (Swabe, 1999). The horse was important in Greek and Roman civilization because members of society relied on it for military and commercial purposes. Earlier (between 383 BC and 322 BC), Aristotle, known as the "Father of Veterinary Medicine," was a powerful figure in Greek culture. Aristotle's publications covered a wide range of topics, including physiology, comparative anatomy, and disease.In works such as HistoriaAnimalium, De Partibus Animalium, De Generatione Animalium, and Problematicum, he contrasted animal and human anatomy, physiology, and illness (Zerobin, 1998). Hippocrates had a significant impact on both veterinary and herbal medicine (460-377 BC). He developed the humoral theory and authored Corpus Hippocraticum, in which he described over 200 plants.

Herbal medicine is being employed as a whole system of treatment by herbalists and as a supplementary therapy by medical experts. Regardless of how herbs fit into the practise of medicine, there is typically some guiding theory at work for their prescription. According to modern herbalists, there are three major principles that underpin herbal use: (i)scientific herbal medicine, or Phytotherapy—this is often reductionistic, researching herbs and illnesses in isolation in order to comprehend them as molecular interactions that can be studied more easily than complete systems. Evidence-based therapies are commonly used by phytotherapists; (ii) Heroic—in this theory, disease is generally viewed as an accumulation of poisons that worsens with age. The treatment focuses on detoxification and limiting one's exposure to pollutants. The herbs utilized in this tradition are potent, beginning with laxatives, diuretics, and diaphoretics (iii) Traditional medicine—The most comprehensive of the traditions. Wise Woman medicine, Native American medicine, Chinese medicine, and other cultural medical systems are examples of traditional medicine and views the organism, restoring health with basic herbs, physical exercise, diet, and mental support (Babu *et al.,* 2017; Singh *et al.,* 2017).

APPLICATIONS OF SELF-MEDICATION

Health-maintenance programmes are adaptable, but they are not without flaws. The capacity to properly self-medicate necessitates a complex combination of intrinsic behavioral skills and refinement gained via learning (experience). It is not proper to abandon sick animals, even if they are free roaming, in the expectation that they would find a method to self-medicate, especially naive or domesticated animals. The greater the number of opportunities for animals to understand the consequences of their behaviors, the better. Domestication has not chosen individuals based on their capacity to self-regulate, and the domestic setting frequently gives minimal chance for trial and error, exposure to potentially harmful bioactive compounds, or gaining knowledge through other people's observations. Nonetheless, consider-

Figure 2. Chimpanzee sucks on the bitter pith of Vernoniaamygdalina (bitter leaf) in Tanzania. (Courtesy Michael Huffman)



ing the scarcity of studies in this field, the examples shown here show that domestic animals maintain a surprising breadth of self-medicating abilities.

Understanding how animals seek to self-medicate is critical if we are to create optimal self-regulation circumstances. Hedonic feedback can explain a lot of the self-medication we witness. This guarantees that animals rarely seek to eat very harmful chemicals and instead favor ones that provide immediate positive feedback. When it comes to finding relief from discomfort, hedonic feedback guarantees that animals employ safer, less potent "treatments" and only on rare occasions succumb to the harsher, frequently more poisonous medicines. This suggests that long-term moderate self-regulation will be more prevalent than spectacular therapeutic efforts including heavy drugs. Individuals are prone to intoxication and even addiction when they consume drugs that give a "feel good component." Although not covered in this article, both intoxication and addiction occur in both wild and domestic species. The fact that an animal rapidly eats a drug does not imply that the substance is safe to take in infinite quantities.

Chimpanzees and humans have equivalent taste preferences. They favour sweet dishes to bitter ones. Vernonia amygdalina, often known as bitter leaf, is a tiny plant found in Tanzania's Mahale Mountains. Most indigenous animals are effectively kept away by its intense bitterness, while introduced domesticated goats are unable to recognise the hazards; as a result, another frequent name for this plant is "goat killer."

When ill, local chimps seek out this bitter, deadly plant, meticulously stripping off the outer layers of shoots and chewing and sucking the juicy bitter pith. Locals see the plant as a powerful remedy, using it to cure malarial fever, stomachaches, schistosomiasis, amoebic dysentery, and other intestinal parasites.

USES MEDICINAL PLANTS IN ZOONOTIC DISEASES

Gastrointestinal Disorders

The gastrointestinal system was the primary target of EVM, accounting for 28 % of total Ethnoveterinary therapy. The most commonly utilised species were *Malvasylvestris* L., *Vitisvinifera* L., and *Matricariachamomilla* L. Apart from *Mercurialisannua* L., which has historically been employed as an anti-constipation agent, numerous plant species appear to be potential gastrointestinal agents (Vanderbrucke*et al.,* 2010). EVM herbs including wormwood (*Artemisia absinthium* L.), elderberry (*Sambucusnigra* L.), yarrow (*Achilleamillefolium* L.), and linseed (*Linumusitatissimum* L. seeds) may help with gastrointestinal issues such colic, indigestion, tympani, and meteorism. On the one hand, they're well-known in human phytotherapy for treating identical ailments (Mayer *et al.,* 2014). Chewing willow by sheep enhances salivary output (Giesecke*et al.,* 1976), which might lead to rumination reactivation, according to EVM reports from Italy and Turkey. However, further pharmacological study is needed to back up these claims. The same may be said about garlic (*Allium sativum* L.), which is most widely used as an antiparasitic but has also been reported as a gastrointestinal agent by EVM in Italy. Garlic was recently studied in sheep to see whether it may help with digestion (Patra*et al.,* 2011), however more fundamental research is needed to back up this claim. In terms of anti-diarrheal, EVM advocates a diverse range of plants, with no continuous repeat of the same species. Because of their tannin content, *Quercus ilex* L. and *Hordeumvulgare* L. may be beneficial (Favre *et al.,* 1993), but more phytochemical understanding and standardised preparations are needed for clinical studies in ruminants.

Malvasylvestris L.

The principal components responsible for mallow's medicinal benefits are mucilaginous heteropolysaccharides, which are found mostly in the leaves (6.0-7.2 %), flowers (3,8-7,3 %), and roots (7,5 %). Leaves and aerial parts were usually provided orally and were thought to be beneficial in cases of numerous digestive disorders, such as abdominal colic, tympanism, reactivation of rumination in small and large ruminants, nonspecific digestive issues, diarrhoea, and constipation (Mayer *et al.,* 2014; Singh & Navneet, 2017b).

Matricariachamomilla L.

A sesquiterpene-containing essential oil and flavones are the main components of chamomile flowers. Chamomile flowers and aerial parts were mostly used in EVM as a decoction or infusion to alleviate cattle digestion issues and colic discomfort. Scientific literature and veterinary phytotherapy textbooks and manuals (Wynn & Fougère, 2006; Mayer *et al.,* 2014) support the usage.

Dermatological Disorders

Plant species that have been indicated for the treatment of dermatological problems, notably wound and ulcer preparations, may also could treat claw disorders.EVM lists three herbs that are effective against cow ringworm. *Ilex aquifulium* L. and *Rhamnuscatharticus* L. appear to have a more ceremonial function, but *Lupinusalbus* L. is the sole plant that may be applied directly to the skin. Although cow ringworm isn't as common as human ringworm, it's nonetheless a serious zoonotic fungal illness that need treatment (Havlickova*et al.,* 2008).In EVM (Full form), Broadleaf Plantain (*Plantago major* L.) was widely discussed as a vulnerary medicine. Veterinary phytotherapy books and manuals, as well as phytochemical investigations, appear to support its medical use. As a result, because there is presently little clinical research concerning veterinary usage, a specific veterinarian assessment would be required. Mallow and St. John's wort (*Hypericumperforatum* L.), both well-known in EVM and listed as vulnerary medications in scientific literature, are examples of this (Mayer et al., 2014). Although respiratory diseases are not a major problem in organic dairy farming, they are a major cause of antibiotic usage in conventional farms (Sivula*et al.,* 1996) and in other livestock species such as chickens and pigs. In EVM, the most common respiratory agents are mallow and chamomile. Antimicrobial characteristics may justify their usage, although more research into the impact on the respiratory system is needed. Inhaling chamomile oil has been shown to have positive effects in people (Saller*et al.,* 1990). Given the particular toxicity of cardiac glycosides contained in the plants, the widespread usage of *Helleborus*sp. in EVM comes as a surprise (Slifman*et al.,* 1998).*Helleborus* spp. roots or branches are put beneath the skin of ill animals in Italy, Romania, Serbia, and Turkey to cure respiratory disorders. Hellborus has been used as an immunostimulant (Nueleanu, 2008; Maior&Dobrotă, 2013).

Scrophulariacanina L.

This plant species has been used to heal dermatological issues, as well as cuts and ulcers, as well as claws and hoofs, according to EVM. Iridoid glycosides, a component of Scrophulariaceae, may have a function as active principle, however there is little published evidence (Stevenson *et al.,* 2002; Tundis*et al.,* 2014).

Pinushalepensis L.

According to contemporary study, the traditional usage of has a scientific basis, conifer resins for wound and ulcer therapy. The needles, twigs, and buds of the Aleppo pine have antibacterial action against a variety of bacterial diseases (Sipponen*et al.,* 2008; Sipponen*et al.*, 2012; Clark *et al.*, 2014)

Antiparasitic Products

The cost of treating ruminants with anthelmintics in Europe is estimated to be over EUR 53 million per year (Ayaz*et al.,* 2008). The rise in drug resistance necessitates new approaches in both conventional and organic agriculture. Furthermore, gastrointestinal parasites pose a significant risk, particularly to organic sheep and goat production (Mayer *et al.,* 2014).EVM identifies white lupin (*Lupinusalbus* L.) and cade (*Juniperusoxicedrus* L.) as the most potential anti-parasitic plants against ectoparasites. White lupin seeds are cooked and applied to the skin of animals, most likely owing to the alkaloid's richness of the bitter variants of this plant (e.g., lupanin) (Wasilewko&Buraczewska, 1999), and are apparently useful

as crop parasite repellent and aphicide (Edwards & Singh 2006;Adhikari*et al.,* 2012). Cade essential oil has been shown to be helpful against red mites in poultry (George *et al.,* 2010). *Nicotianatabacum* L., a kind of cultivated tobacco, is also used to fight ectoparasites. Given the pharmacological and toxicological qualities of nicotine, the plant's main alkaloid (Millar &Denholm 2007), further research is needed to determine if this plant may be used safely. Italian EVM uses infusions of Fraxinusornus L. branches, leaves, and flowers to treat ectoparasites and diarrhoea. Broilers have been shown to have anti-coccidial capabilities (Papazahariadou*et al.,* 2010), although the usage in (anthelmintics) and (ectoparasites) indications requires more research. *Rutachalepensis* L. and *Rutagraveolens* L. are antiparasitic plants used in EVM. *R. chalepensis* is mostly used against ruminant endoparasites. There is early evidence, particularly in regard to their potential usage against endoparasitosis (Calzada*et al.,* 2006), but further research is needed, particularly in regard to their rumen metabolism.

Allium sativum L.

In EVM, the effects of garlic bulbs are well established. *In vitro* and *in vivo* activity on several endoparasites (round and flatworms, flagellates) has been demonstrated (Zenner*et al.,* 2003; Singh *et al.,* 2009). Garlic was also shown to have some activity against chicken mites when applied topically (Birrenkott*et al.,* 2012). In a textbook on veterinary phytotherapy, *Allium sativum* L. is cited as an anthelmintic and antiprotosoic, but additional study is needed (Santosh *et al.,* 2012), particularly clinical veterinary trials (Mayer *et al.,* 2014).

Artemisia absinthium L.

Leaves of wormwood and aerial parts are used in EVM to combat ecto- and endoparasites in cattle. Wormwood may be effective as an anthelmintic (Tariq *et al.,* 2009; Amirmohammadi *et al.,* 2014), however its application as an ectoparasitic or repellant agent has to be shown (Gonzalez-Coloma *et al.,* 2012).

Disorders of Female Genital and Udder

Mastitis and vaginal internal infections occur predominantly after calving and represent a significant financial loss for organic dairy cows, as the withdrawal period after antibiotic treatment is twice as long as in conventional farming (Fall &Emanuelson, 2009; Ivemeyer *et al.,* 2014).

Internal Female Genital Organs

Mallow is used as an anti-infective and antiseptic after childbirth in Spain, while mallow decoction is used to evacuate the placenta after childbirth in Italy. In both circumstances, a decoction or infusion is supplied orally to the animals. More study is needed to back up this application of mallow.

Mastitis

Mastitis is a worldwide endemic disease and potentially fatal mammary gland infection that causes inflammation of the udder tissue and mammary gland. Mastitis is caused by bacteria that infiltrate the mammary gland cell. Swelling and heated udders, lack of appetite, and fever are frequent symptoms of

the condition (Cho *et al.,* 2015) Mastitis-affected cows cannot be milked on a regular basis because the mammary gland cells have been destroyed. Furthermore, clot formation is typical in mastitis milk; this is driven by pathogenic bacteria-produced enzymes such as coagulase, which allow the conversion of fbrinogen to fbrin.Contagious microorganisms that survive and proliferate on the skin and teat wounds, such as *Streptococcus agalactiae, Staphylococcus aureus,* and *Strep. dysgalactiae*, as well as environmental microorganisms such as S *uberis*, *Escherichiacoli*, and other coliforms, are among the primary mastitis-causing pathogens. Tese bacteria enter cows' mammary glands through their teat canal, where they colonise, grow, and emit toxins that harm the cells of the mammary gland. Infection is detected by a rise in lactic dehydrogenase (LDH) activity inmilk. The inflammatory responses are generated shortly after infection; for example, the number of somatic cells and levels of inflammatory cytokines including tumour necrosis factor (TNF)-, interleukin (IL)-6, and IL-8 rise in milk (Yang *et al.,* 2019).

Aloe barbadensis

Aloe vera is commonly used to enhance the immune system in both people and animals without causing any negative side effects. Aloe vera gel helps to speed up the healing process at the wound site. Thangaduraiet *al.,* (2017) investigated the efficacy of herbal combinations in the treatment of mastitis. This decision was made to reduce the expense of therapy for cowbreeders. Aloe vera, lime, and turmeric powder were used in the experiment. The study's findings were described as "effective mastitis management strategies." Mastitis milk has a high somatic cell count, conductivity, and pH when compared to antibiotic control (Thangaduraiet *al.,* 2017). The author found that a combination of these herbs is effective in the treatment of mastitis.

Allium sativum

Herbal medicine, such as garlic cloves (*Allium sativum*), is commonly used to cure a number of disorders (Dishadet *al.,* 2008). As many cases of mastitis as feasible were found to be treated, yielding a positive result. Due to the active element 'allicin' in garlic, the study found that using it increased the quantity and percentage of lymphocytes, increased the composition of milk and blood parameters, and improved the immune system (Ibrahim *et al.,* 2016). As a consequence, it produced comparable results as Dilshad and colleagues' investigation (2008). Garlic, together with Vitamin E + Se and lemon, has been shown to be beneficial in the treatment of subclinical mastitis.

Angelica dahurica and Rheum officinale extracts

The authorised herbs Yi-Xiong-Tang (YXT), produced from the extracts of *A. dahurica* and *R. officinale,* have been shown to have wound healing, anti-inflammatory, and antibacterial properties. Yang and colleagues investigated the efficacy of YXT against bovine mastitis (2019). As a consequence, bacteria in mastitis milk decreased, indicating that YXT had active antibacterial effects. After treatment with YXT, the amount of inflammation in mastitis milk returns to normal, indicating that YXT has anti-inflammatory properties (Yang et al., 2019).

Curcuma domestica

*Curcuma domestica*has been discovered to have antibacterial properties, making it effective in the treatment of mastitis.The findings were backed up by prior research that showed Curcuma domestica's antibacte-

rial action against Methicilin-resistant *Staphylococcusaureus*(MRSA) Mun *et al.,* (2013) and *E. coli* de Oloveira *et al.,* (2018). *Ageratum conyzides*, *Muntingacalabura*, *Piper betle*, and *Curcuma domestica* were found to be effective alternative treatments for mastitis infection.

Mentha essential oil

Essential oils were used as a novel target that was both safe and effective against a variety of diseases. Essential oils extracted from plants have been discovered to have strong antibacterial and healing properties (Grzesiak *et al.,* 2018). Mentha is a mint family plant (Lamiaceae). Much prior research had demonstrated the usefulness of antibacterial characteristics found in the mint family (Golestan *et al.,* 2016; Ramos *et al.,* 2017). Harvoth&Koskova (2017) investigated the antibacterial activities of essential oils from three mint species: *Menthaspicata, Menthapiperita*, and *Menthaarvensis* against *S. aureus*. According to the results of this study, the three mentha essential oils effectively inhibited Staphylococcus strains. In a study conducted by Imai et al., the efficacy of all three mint families was confirmed (2001). All three essential oils were found to have different effects due to their various contents.

Origanumvulgare

Origanumvulgare (Oregano) is a mint-family herb plant (Lamiaceae). Cho and colleagues (2015) conducted a study to assess the efficacy of oregano essential oil (OEO) therapeutic activity reaction against clinical mastitis caused by *S. aureus* and *E. coli*. The advantages acquired from the outcome in battling mastitis infection with antibacterial activities of OEO are validated by numerous prior investigations. These include enhanced membrane permeability (Lambert *et al.,* 2001), slowed the growth of bacteria and increased the number of somatic cells in milk as well as white blood cells (De Souza *et al.,* 2006) (De Souza *et al.,* 2006). Other positive results reported from this trial include an improvement in udder health and the absence of *S. aureus*and *E. coli* in milk (Sharma &Jeong, 2013). It was demonstrated that the findings of this study supported OEO as an alternate therapy for mastitis.

Brucellosis

Brucellosis is an infectious illness caused by *Brucellaabortus* that has a significant morbidity in animals (Grillóet *al.,* 2006). Humans often get the disease by eating or drinking contaminated animal products, direct contact with infected animals, or inhaling airborne pathogens; however, the vast majority of infections are caused by consuming unpasteurized milk or cheese (Terwagne&Collaghan, 2012). Trade in livestock, particularly cattle, has declined as a result of increased infections, unanticipated abortions, and low lactation leading to reduced milk production, and giving birth to unhealthy offspring (Gul& Khan, 2007). David Bruce, an army surgeon, was the first to discover the link between Brucella and brucellosis. From 1886 through 1887, he isolated germs from the spleens of patients in Malta. Brucellosis is still one of the most frequent zoonosis in the world, with over 500 000 patients identified each year, the majority of whom reside in impoverished nations. *Brucellasuis* (*B. suis*), *Brucellamelitensis* (*B. melitensis*), *Brucellaabortus* (*B. abortus*), and *Brucellacanis* are four distinct *Brucella* species that can be harmful to humans (Whatmore*et al.,* 2016).*Juniperusoxycedrus L., Menthapiperita, Origanummajorana, Myristicafragrans, Cinnamomumverum, Citrus limon, Nigella sativa, Crocus sativus* L., and *Vitex pseudo-negundo* have antibrucelleosis action (Mohsen *et al.,* 2018).

Allium sativum

The impact of chloroform *A. sativum* extract on *B. melitensis* (Rev1) and *B. abortus* was studied by Shapoury et al. (2004) In that investigation, chloroform A. sativum extract was shown to suppress the growth of *B. melitensis* and *B. abortus* at 37°C for 3 days at dilutions of 1:10 to 1:160. After 2 h of development at 4°C and 37°C, the *A. sativum* extract was shown to inhibit both *Brucella* species (Shapoury*et al.,* 2004).

Berberisintegerrima

Recent research looked at the effect of *Berberisintegerrima* active components on B. abortus (RB51) after 17 h of incubation at 37°C. Finally, at 620, 500, 250, and 120 g/mL, the MICs of palmatine, berberine, columbamine, and jatrorrhizine were 6.25, 1.56, 3.12, and 0.78 mm, respectively (Azimi*et al.,* 2018)

Caraway (Carumcarvi L.)

This plant's essential oil, at 0.3-2 mg/mL, has been shown to suppress *B. abortus*isolated from cattle (Singh *et al.,* 2015).

Citrulluscolocynthis

Citrulluscolocynthis is a desert and perennial plant that spreads in African, Arab, and Indian nations, according to Mahendiran and Umavathi. When mature, the fruits of this plant are meaty with dark green markings and generally yellow. At 25 mg/mL, an ethanol extract of *C.colocynthis*was able to create a growth-restraining zone 15 mm in diameter for 24 hours under (35 2) °C (Mahendiran&Umavathi, 2011)

CONCLUSION

Ethnoveterinary medicine is a branch of ethnobotany concerned with the study of traditional remedies. Ethnoveterinary methods are as old as the domestication of numerous livestock species when it comes to animal healthcare. For most of history, the growth of veterinary botanical medicine, the oldest kind of veterinary medicine, has followed a parallel path to that of human medicine. Plant-based herbal medicine has experienced a variety of conceptual modifications over time, yet its tone has stayed mostly same from antiquity to the present. They include beliefs, knowledge, behaviours, and abilities related to cattle health and management. It is used as a treatment and prevention approach for a variety of cattle illnesses. Herbal treatment strives to not only cure the underlying cause of the illness, but also to reverse aberrant symptoms and restore the animals' health and vigour.

Table 1. List of some importantmedicinal plants used in various zoonotic diseases

Diseases	Botanical name (Family)	Parts Used	Mode of Administration
	Acacia nilotica L. (Fabaceae)	Bark	To treat dysentery, a bark extract is given to animals orally twice a day for 10-20 days.
Jaundice	*Acacia nilotica* L. (Fabaceae)	Flower	To treat jaundice, 200 g flower is finely ground and combined with 250 mL water. The resulting solution is administered orally twice day for 15-20 days to the animal.
	Adhatodavasica Nees. (Acanthaceae)	Leaves	To cure diarrhoea and dysentery, leaf juice is blended with an equal amount of *S.cumini* bark juice and given three times a day for one week.
Sun burn	*Aeglemarmelos* (L.) Corr. (Rutaceae)	Leaf, Seeds	500 g fresh leaves, ground into a paste, and combined with 100 mL *Ricinuscommunis* seed oil This paste is applied to the sun-burned skin till it heals.
Removal of ectoparasites	*Allium cepa* L. (Liliaceae)	Bulb, Leaf	The onion bulb is finely ground and combined with 100 mL mustard oil and 25 g *Musa paradisiaca* leaf ash. The resulting combination is applied topically to the skin to remove ectoparasites.
Foots infection, Rheumatism	*Argemonemexicana* L. (Papavaraceae)	Leaf, Fruit	The juice is collected from the leaves (100 g) and fruits (100 g) and applied to infected feet. The same juice is administered to the bodily areas of cattle to relieve rheumatic discomfort.
Arthritis	*Asparagus racemosus* Wild. (Liliaceae)	Root	For the treatment of arthritis in cattle, 500 g root powder was administered with milk for one month.
To enhance lactation	*Asparagus racemosus* Wild. (Liliaceae)	Root	For one month, 500 g root powder was administered with milk.
	Azadirachtaindica A. Juss.(Meliaceae)	Bark	500 g of *A.indica* bark and 250 g of *A.nilotica* bark are ground and mixed with water. The paste is then applied to the wounds until they heal completely.
	Bambusaarundinacea (Retz.) Wild. (Poaceae)	Leaf, Rhizome	The cattle with diarrhoea are fed an equal amount of rhizome and fresh bamboo leaf paste twice a day for seven days.
Easier delivery	*Bambusaarundinacea* (Retz.)Wild. (Poaceae)	Leaf	The leaves (100-200 g) are fed to pregnant buffalo twice a day for a month to make birth simpler.
Dysurea, paralysis	*Buteamonosperma* (Lam.)Taub. (Fabaceae)	Flower	Flowers are decocted and given to cattle three times a day for a month to alleviate dysuria and paralysis.
	Calotropisprocera (L.) R. Br (Asclepiadaceae)	Flower	Flower paste (50 g) combined with jaggery (100 g) and fed to animals for easiness.
Constipation	*Cassia fistula* L. (Fabaceae)	Leaf, Ripe pod	The young leaves are used as a purgative after being cooked. For purgative purposes, ripe pod paste is also given.
	Cassia fistula L. (Fabaceae)	Pod	In the case of indigestion, cattle are given the pod paste twice a day with wheat bread.
Loose motion	*Coriandrumsativum* L. (Apiaceae)	Seed, Leaf	To treat loose motion, the seed powder is combined with *Lawsoniainermis* leaf paste and administered twice daily for seven days to the animal.
	CynodondactyIon (L.) Pers. (Poaceae)	Aerial plant	The aerial plant is fed as fodder to increase lactation and milk quality (0.3 kg per day).
Stop bleeding	*Dalbergiasissoo* Roxb. (Fabaceae)	Leaves	To successfully halt bleeding, 100 g leaf juice is administered twice or thrice a day for one week.
Cough,Cold	*Datura metal* L. (Solanaceae)	Ripen fruit	To cure a cold, 100 g of ripe frits are ground into a paste and fed to cattle once a day for 7 days.
Wounds	*Datura metal* L. (Solanaceae)	Leaf, Root	To halt bleeding from wounds and promote early healing, a paste made from 300 g fresh leaves and 200 g roots is given to animals once daily for seven days.
Fever	*Delonixregia* L.(Fabaceae)	Bark	For the treatment of fever, a bark extract is administered twice day with black pepper and garlic till cued.
	Ecliptaprostrata L.(Asteraceae)	Leaf	Grinded fresh leaves are cooked in mustard oil. The resulting paste is applied to wounds twice daily for 10-15 days to promote early healing.
Intestinal worm	*Feroniaelephantum* L. (Rutaceae)	Leaf	In the event of intestinal worms, fresh leaves are ground thoroughly and combined with 500 L of water before being fed to cattle once daily for 10-20 days.
Stomachache	*Ficusbenghalensis* L. (Moraceae)	Root	About 100 g root is finely ground and fed to cattle suffering from stomachaches once a day for 3 to 4 days.
Tonsils	*Ficusreligiosa* L. (Moraceae)	Leaves	Tonsil cures are made from the juice of the leaves.
Twitching	*Hibiscus rosa-sinensis* L. (Malvaceae)	Bark	In the event of twitching, 150-200 g of bark is finely ground and administered with one litre of water twice day till total relaxation is achieved.
	Holopteliaintegrifolia (Roxb.) Planch. (Ulmaceae)	Leaf	Ecto-parasites are removed by applying leaf juice to the skin.
	Madhucaindica J.F. Gmel (Sapotaceae)	Flower	To cure cow fever, 100 g flower paste, 250 g jaggery, and 50 g water are combined and given twice daily for seven days.
Indigestion	*Mangiferaindica* L. (Anacardiaceae)	Fruit	In the case of indigestion, the paste is made from 50 to 100 g fruit and fed to cattle once or twice daily for seven days with wheat bread.
	Menthaarvensis L. (Lamiaceae)	Leaf	To cure fever, the paste is made from 250 g *Menthaarvensis* leaves and 200 g *Centellaasiatica* leaves and fed to cattle twice a day for 7 days.
	Moringaoleifera Lamk. (Moringaceae)	Leaves	For rapid treatment from diarrhoea and dysentery, cattle are fed 100-200 g leaf paste twice daily for three to five days.
Body heat	*Musa paradisiaca* L. (Musaceae)	Leaf, Root	To lower body heat in cattle, young leaves and roots are fed with feed for one week.
	Ocimumgratissimum L. (Lamiaceae)	Leaf	Externally, leaf paste is applied to cattle's skin to kill ectoparasites.
	Ocimum sanctum L. (Lamiaceae)	Leaf	Fresh *O. sanctum* leaves (350 g) are cooked in water (200-250 mL) and the resulting decoction is used to treat cough and colds. Fresh *O. sanctum* leaves (350 g) are cooked in water (200-250 mL) and the resulting decoction is used to treat cough and colds.
	Oryzasativa L.(Poaceae)	Grain	Black gramme, black salts, and black pepper are cooked with rice grains. To improve lactation in cattle, offer the prepared dish once or twice a day for one month.
	Psidiumguajava L. (Myrtaceae)	Leaf	To cure fever, one litre decoction of fresh leaves is taken twice daily till recovery.
	Ricinuscommunis L. (Euphorbiaceae)	Seed	In the event of cattle constipation, around 50 g seed is administered orally with feed for 7 days.
Joint pain	*Syzygiumcumini* (L.) Skeels. (Myrtaceae)	Bark	In the event of joint discomfort, an equal amount of bark from *S.cumini* and *A.indica* is cooked in water and the resulting decoction is applied to the afflicted joints.
Swelling	*Tamarindusindica* L.(Fabaceae)	Leaves	Fresh leaves (400-500 g) are prepared in water and tied to the afflicted portion of the body to relieve swelling until it is completely gone.
Hydrophobia	*Tegetuserecta* L. (Asteraceae)	Leaf	About 20-40 g leaves are cooked in 500 mL water, and the resulting decoction is administered to cattle suffering from hydrophobia once a day for a month.
	Tribulusterrestris L. (Zygophyllaceae)	Leaves	In the case of colic and persistent cough, animals are fed fresh leaf juice.
	Vignaradiata (L.) R. Wilczek (Fabaceae)	Seed	Cattle suffering from cough and cold are fed 250 g seed powder mixed with 100 mL *A. hypogea* oil twice daily for 7 days.
Diarrhoea and dysentery	*Vitexnegundo* L. (Verbenaceae)	Leaves	To treat diarrhoea, cattle are given dried leaves mixed with grain for a week.
Physically disability	*Zingiberofficinale* Rosc. (Zingiberaceae)	Rhizome	For 15 days, 100 g fresh rhizomes are cooked in half litre cow milk and fed twice a day to physically disabled animals.

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Chapter 4
Plant Extracts With Antibiotic Effect

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ABSTRACT

This chapter tries to describe the most important plant extracts and their bioactive compounds which determine the antibiotic activity. Pharmacological assays performed for each plant extract are presented, including the minimum inhibitory concentration (MIC) as the most used experimental method to determine antimicrobial activity. Also, the effective associations between classic antibiotics and plant extracts with antibacterial are presented. The mechanisms of action are deeply explained to the extent that they are known and discovered by in vitro and in vivo studies. Plant-derived compounds have different mechanism of action as antibiotics. They can have other target sites than traditional antimicrobials and subsequently having different mechanisms of action against microbes. Ultimately, this chapter tries to be an invitation to use plant extract as an alternative to chemical, synthetic antibiotics, or used complementary, synergistic for better therapeutically results.

INTRODUCTION

Bacterial infections are a major cause of human pathologies. Massive use of antibiotics led to developing

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resistance against them, which is another problem affecting public health. To fight against the lack of the new substances with antibiotic effect, and against the increasing antibiotic resistance, plants could be a potential solution in the future. Medicinal plants produce a variety of secondary metabolites that have an important role in adaptation to the environment, providing them with effective defense mechanisms to control pests and pathogens. Plants provide a great biodiversity, including about 374,000 plant species, of which about 290,000 of them have secondary metabolites. Among these natural compounds are essential oils, flavonoids, coumarins, tannins, quinones, alkaloids, lectins, polypeptides, thiosuflinates and others, that have potential therapeutic action to fight against bacteria (Kokoska *et al*., 2019; Alvarez-Martinez *et al*., 2020). They have many advantages like lesser side effects, more patient approval, and are less costly.

Many *in vitro* studies have showed the antibacterial effect of some plant extracts, based on measuring the minimum inhibitory concentration, which is the lowest concentration of a substance that inhibits 90% of the bacterial growth, as the most used indicator of the antimicrobial efficacity (Drusano *et al*., 2004). Scientific studies have been performed to verify the antibacterial potency of plants against all kinds of bacterial cultures, including biofilms. Moreover, two plant extract products have received approval from the U.S. Food and Drug Administration (FDA) as antibacterial drugs: Veregen, based on green tea leaf extract, which contains epigallocatechin gallate, indicated for genital and perianal warts, and Fulyzaq or Mytesy, extracted from the dragon's blood, for the treatment of diarrhea in cases of patients with HIV antiretroviral therapy (Wu *et al*., 2020).

For a better efficacy, in pharmacological studies plants are used as extracts. During extraction, the active compounds from medicinal plants are separated from the other inactive components, based on their solubility in different solvents. The methods of standard extraction are decoction, infusion, maceration, percolation, digestion, or Soxhlet extraction, and the final products obtained are decoctions, infusions, macerates, essential oils, aromatic waters, tinctures, semisolid, and dried extracts. Chassagne *et al*. (2021) noticed that among different plant extracts, crude extraction in methanol was the most used type of extraction encountered in studies, while leaves were the main plant organ used for extraction.

The purpose of the chapter is to present the most important plant extracts with antibiotic effect, based on their efficacy against bacteria, proved by recent, in vitro studies, together with their mechanism of action, which can be used as promising alternative to common antibiotics.

BACKGROUND

Microbial resistance to antibiotics has led scientists to target new molecules to discover substances that can fight bacteria. Plants are a huge and inexhaustible source of bio compounds with pharmacological activities, including antibacterial. Plant extracts are used for centuries in different traditional medicines, and nowadays included in various clinical studies for studying different therapeutically effects concerning human pathologies. Different yeasts and plant extracts were used since antiquity to treat infections. For example, Egyptians used to apply mouldy bread to infected wounds. However, common bacterial infections were the major cause of human death, and it was until 19th century that scientists discovered few antibacterial substances in action. Alexander Fleming accidentally discovered penicillin, in a culture of a *Penicillium notatum* mould, proved to be extremely effective against *Staphylococcus* bacteria. The treatment with this first mass-produced antibiotic was hugely successful, and a huge discovery for humankind, as it saved many soldiers' lives in the Second World War, in the field and in hospitals.

Plants extracts are rich in many secondary metabolites such as polyphenols (flavonoids, quinones, tannins, coumarins), terpenoids (from essential oils), alkaloids, isothiocyanates, glucosinolates, lectins and polypeptides, which have been found *in vitro* to have antimicrobial properties against different types of bacteria. Many studies have been conducted in different countries to prove the efficiency of phytochemicals for therapeutic treatments. Pancu *et al*. (2021) observed that "between 1986 and 2006, more than 100 antimicrobial drugs were approved for clinical use, 75 being of plant origin".

CHEMICAL STRUCTURE OF BIOACTIVE COMPOUNDS

Herbal antibacterial compounds can be divided into several categories, as phenolic compounds, quinones, flavonoids, tannins, glucosinolates, thiosulphur compounds, lignans, terpenoids and alkaloids, as well as another described below:

Phenolic and Polyphenolic Compounds

They are the most common secondary metabolites of plants; the term phenol defines phenyl ring compounds substituted with one or more hydroxyl groups, and the term polyphenols defines compounds with at least two phenyl rings substituted with one or more hydroxyl groups, including their functional derivatives. Constituents with diversified chemical structure, phenolic and polyphenolic compounds are represented by simple phenols and benzoquinones, phenolic acids, stilbenes, hydroxycinnamic acids, flavonoids, coumarins, lignans, anthraquinones, naphthoquinones. They are mainly found in conjugated form with simple, acylated or protein-bound bases.

Simple Phenols and Phenolic acids

Some of the simplest phyto-compounds with antimicrobial effects are catechol and floroglucinol, characterized by the presence of two or three groups - OH, respectively, with toxic effects on microorganisms. Simple phenolic compounds often have alcohol, aldehyde, and carboxylic groups, such as eugenol and vanillin, compounds well known for their antibacterial activity. Phenolic acids are derived from cinnamic acid and are widespread compounds in the plant kingdom. Cinnamic acid is a precursor for the synthesis of more complex phenolic compounds such as p-coumaric acid and caffeic acid. Phenolic acids have antimicrobial potential due to the presence of numerous groups -OH or methoxy (-OCH3), with cytotoxic effects on infectious agents. Caffeic acid in the form of 3- caffeoylquinic ester, known especially as chlorogenic acid, has been shown to effectively inhibit the growth of bacterial pathogens, *Shigella dysenteriae* and S. pneumoniae at MIC values between 20 and 80 µg / mL. (Lou *et al*., 2011).

Quinones

Quinones are 1,4-diceto-cyclohexa-2,5-dienic derivatives (p-quinones) or 1,2-diceto-cyclohexa-3,5-dienics (o-quinones), with conjugated double bonds. Structurally, these compounds have carbonyl groups grafted on a benzene ring (benzoquinone), on bi or polycyclic aromatic hydrocarbons, simple (e.g., naphthoquinone, anthraquinone) or condensed (naphthodiantrone), or on the structure of terpenes. Nitrogen heterocyclic compounds rarely have a quinone structure. The most common natural quinones

are hydroxylated and are found in plants in reduced form (naphthohydroquinone), but in the extraction process they hydrolyze and turn into naphthoquinones. These compounds can form irreversible complexes with amino acids in proteins, thus causing antibacterial activity (Abad Martinez *et al*., 2005, Stern *et al*., 1996, Castro *et al*., 2013). The 1,4-naphthoquinone has significant antibacterial activity in vitro against gram-positive and gram-negative bacteria.

Flavonoids

They are natural polyphenols, type C_6-C_3-C_6, characterized by the presence of the benzopyran nucleus substituted with phenyl radical. Depending on the degree of oxidation of the molecule and the site of phenyl insertion, there are several categories of flavonoid compounds, namely: flavones, flavonols, flavanones, catechins, flavanonols, isoflavones, chalcones, anthocyanins. The diversity of these compounds is also explained by some structural chemical modifications such as hydroxylation, methylation, acylation, glycosylation. Some flavonoids, such as hesperidin, hesperetin, naringin, and naringenin, have antibacterial and antifungal activity. Relatively recent in vitro studies have shown the antibacterial action of flavones such as kaempferol, luteolin, myricetin, including against MRSA (Xu & Lee, 2001). The antibacterial activity is due to the ability of these compounds to affect protein synthesis and the integrity of the bacterial cell wall and through synergism with some antibiotics (Tsuchiya *et al.*, 1996; Cowan, 1999).

Tannins

They are derived from polyphenol carboxylic acids or phenyl benzopyran. Structurally, they are hydrolysable tannins and proanthocyanins (condensed tannins). Hydrolysable tannins are esters of gallic acid and ellagic acid or their derivatives with carbohydrates (glucose or another oasis) or a cyclitol. Proanthocyanins are polymers of flavan-3-ols (e.g., catechin) and flavan 3,4-diols bound by an interflavonoid bond that is not hydrolysable. Tannins have the ability to complex with proteins by ionic reaction and / or hydrogen bonds and also by covalent bonds. Antibacterial action is also based on this mechanism, especially against gram-negative germs (Haslam, 1996; Stern *et al.*, 1996; Cowan, 1999).

Lignans

Lignans and neolignans are composed of great structural diversity and promising antimicrobial activity. Important for therapy are components with the structure of tetrahydrofuran, such as 8-hydroxypinoresinol. This compound isolated from the bark of *Strombosia grandifolia* is very active against *S. pneumoniae, E. coli, S. aureus* and *S. typhi* (Ekalu *et al*., 2019). Carinol, a lignan isolated from *Carissa species*, especially stems and roots, showed considerable antimicrobial activity against four bacteria, *P. aeruginosa, E. coli, Staphylococcus aureus* and *Bacillus subtilis,* with a MIC <1.25 mg / mL (Kaunda & Zhang, 2017). Five lignans (secoisolariciresinol, pinoresinin, eudesmin, lariciresinol and lariciresinol-4-methyl ether) isolated from *Araucaria araucana* (Mol.) showed significant antibacterial activities, the most sensitive being Gram-positive (Céspedes *et al*., 2006).

Glucosinolates and Thiosulfinates

Glucosinolates are a group of compounds whose structure comprises a "p-D-thioglucose" group, a "sulfonated oxime" moiety and a variable side chain derived from methionine, tryptophan, or phenylalanine. When plant tissue is damaged, glucosinolates are hydrolyzed by the endogenous enzyme "myrosinase" or intestinal microflora after ingestion, releasing a range of degradation products, including biologically active isothiocyanates (Mithen *et al.*, 2010). The isothiocyanates resulting from the enzymatic degradation of synigrozide, sinalboside, glucobrasicin act as an antibiotic against gram-positive and negative bacteria. Cysteine sulfoxides (whose prototype is aliin) by cutting or crushing under the influence of the enzyme aliinase are transformed into esters of thiosulfinic acids, whose prototype is allicin. The antibiotic effect is due to the alkylsulfinates formed from sulfoxides, while the alkylsulfides and alkenylsulfenic acids have mainly bacteriostatic action.

Terpenoids and essential oils

Terpenoids are products of secondary plant metabolism, the main constituents of essential oils, secreted in specialized plant tissues. They are composed of isoprene units (C_5H_8) n and can be classified into monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), etc., depending on the number of forming units (Cowan, 1999). Terpene compounds may be hydrocarbons (myrcene, limonene, terpene, pinene, bisabolene, caryophyllene) or oxygenated derivatives including alcohols (linalool, nerol, geraniol, citronellol, terpineol, menthol, borneol, bisabolol, farnesol), phenols, carvacrol, thymol, eugenol), aldehydes (geranium, citral and citronellal), ketones (tagetone, menthone, carvone, thuione, camphor) or ethers (eucalyptol, linalool oxide) and esters (linalyl acetate, menthyl acetate). Depending on the antibacterial coefficient, the compounds with the best activity are phenols, followed by methyl ethers, monoterpenic aldehydes, monoterpenic ketones. The antibacterial properties of these compounds are due to their ability to block the proliferation of pathogens by direct neutralization or by neutralizing their toxins.

Prevalence of Antibiotics in Plants

Chassagne *et al*. (2021) analyzed the antibacterial activities of 958 plants from the literature published until 2019. The authors noticed that "antibacterial effect is found in 51 of 79 vascular plant orders throughout the phylogenetic tree. Most of them are reported within eudicots, with the bulk of species being asterids, while monocotyledons have poor antibacterial activity" (Chassagne *et al*., 2021). The *Lamiaceae, Fabaceae* and *Asteraceae* families were the most represented, while *Cinnamomum verum*, *Rosmarinus vulgaris* and *Thymus vulgaris* were the most frequent species studied for their antibacterial action.

Mechanism of Action

Regarding the intrinsic mode of action of antibacterial bio compounds, Ginovyan *et al*. (2017) emphasized that they "could have other target sites than traditional antimicrobials and subsequently having different mechanisms of action against microbes". Among the ways these bio compounds act as antibacterial are the disrupting of microbial membranes, impairing the cellular metabolism, inhibiting the biofilm formation, reducing the bacterial capsule production, controlling quorum-sensing, or reduction of the microbial

toxin production (Ginovyan *et al*., 2017). Al Sheikh *et al*. (2020) mention that "essential oils from parsley, lovage, basil and thyme disrupt the physiological status of the bacterial cell by causing an increase in cell permeability, leakage of cell constituents, alterations in bacterial cell wall and cell membrane, ATP loss, inhibition of protein synthesis, pH disturbance, intracytoplasmic damage, DNA damage and inhibition of quorum sensing among bacteria" (Al Sheikh *et al*., 2020). Regarding the mechanism of action of cinnamon and its constituents, Vasconcelos *et al.* (2018) noticed that " inhibit bacteria by damaging cell membrane; altering the lipid profile; inhibiting ATPases, cell division, membrane porins, motility, and biofilm formation; and via anti-quorum sensing effects" (Vasconcelos *et al*., 2018). An extensive review performed by Álvarez-Martínez *et al*. (2021) on the full spectrum of plant antimicrobial agents discovered from 2016 to 2021, proved that the most frequent mechanism of antimicrobial effect is the interruption of plasma membrane of bacteria.

It is also important to highlight the synergistic mechanism of herbal compounds with the classical antibiotics, due to decreasing the bacterial resistance, as shown by numerous studies.

PLANTS WITH ANTIBIOTIC PROPERTIES

Mentha piperita L.

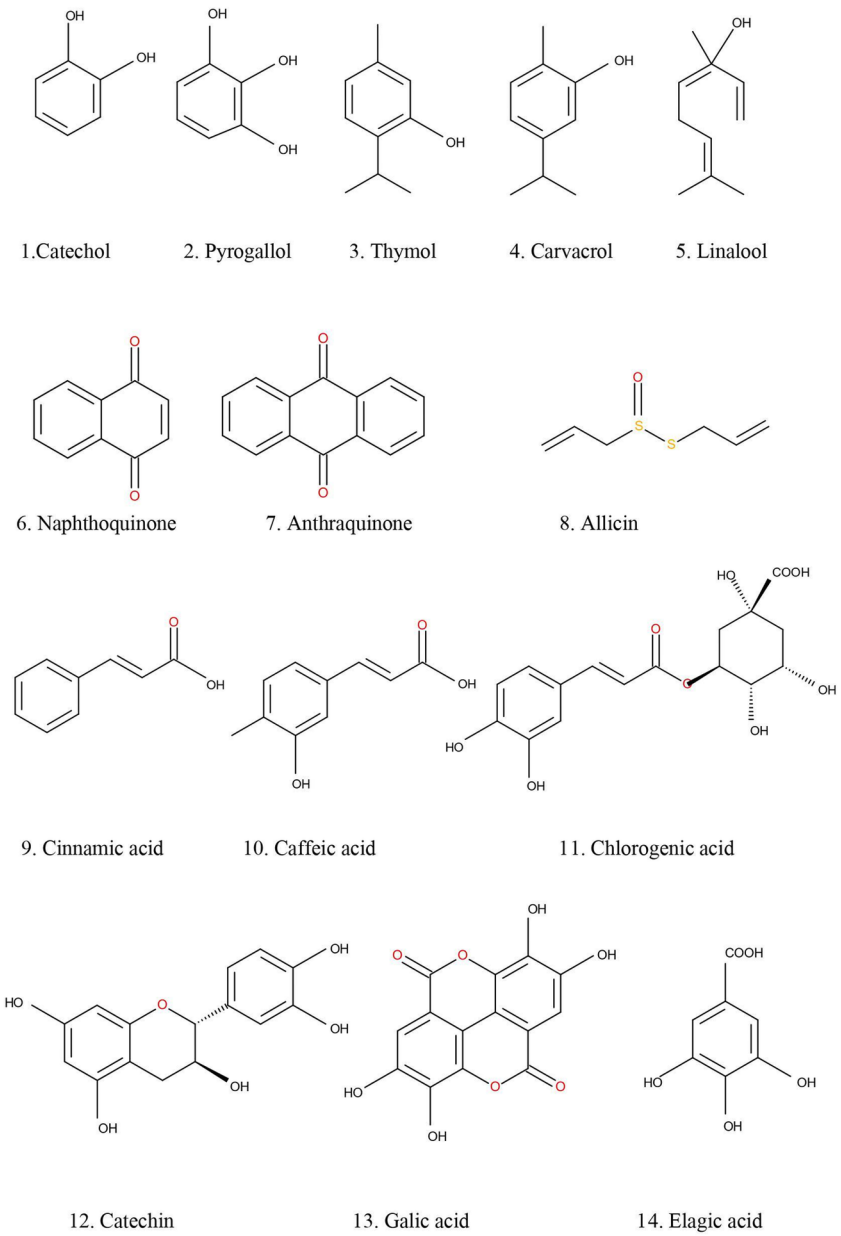
Plant Description

Peppermint is a hybrid between two species: *Mentha spicata* L. (spearmint) and *Mentha aquatica* L. (water mint) and is a perennial plant from the *Lamiaceae* family. It is worldwide cultivated as a medicinal specie for its anti-inflammatory, antidiarrheic, antispastic, analgesic, antifungal, antimicrobial, and central nervous system excitation effects and used for the treatment of a wide range of digestive maladies, musculo-skeletal pains, respiratory disorders, and various infections. The essential oil of peppermint contains mainly menthol, 1,8-cineole, limonene, β-myrcene, β-caryophyllene, menthone, isomenthone, pulegone, carvone, menthyl acetate, and menthofuran (Akhtar *et al*., 2017). Peppermint also has bitter substances, caffeic acid, flavonoids, and tannins.

Biological Activities

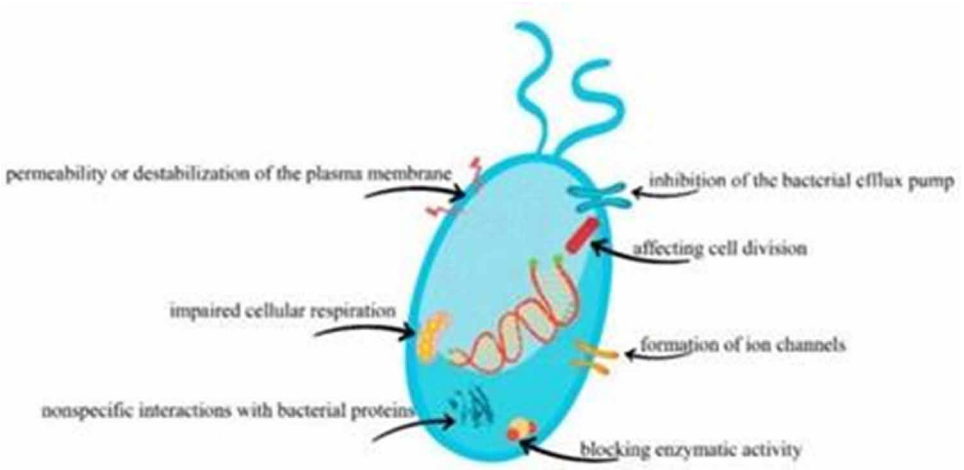
Several studies demonstrated a significant antibacterial activity for peppermint essential oil. Abolfazl *et al*. (2014) noticed an important antibacterial activity of the essential oil, due to the monoterpenes as menthol and menthone, which exerted MICs with an average of 0.5–8 μg/mL in *Staphylococcus aureus*, *P. aeruginosa*, *Streptococcus pneumoniae, E. coli*, *Salmonella typhi* and *Klebsiella pneumoniae* strains. The essential oil from *M. piperita* exhibited antimicrobial effect against *Salmonella enterica*, with an inhibition zone of 9.00 ± 1.00 mm (Valková *et al*., 2021), on *S. aureus, P. aeruginosa*, *E. coli,* and *K. pneumoniae* (Osanloo *et al.*, 2020), and also against *Salmonella typhius*, *Staphylococcus epidermititis*, *S. aureus*, *B. subtilius*, *P. aeruginosa*, and *Klebsiella pneumonia* cultures (Saba & Anwar, 2018). The other biological compounds from peppermint, as phenolics exert antibacterial activity, too. Mahady *et al*. (2005) found that the methanolic extract of mint was active on *Helicobacter pylori* strains, with a minimum inhibitory concentration (MIC) of 25–100 μg/mL. The ethanolic extract of peppermint which contains gallic, *p*-coumaric chlorogenic, neochlorogenic, ferulic, and rosmarinic acids, epicatechin,

Figure 1. Chemical Structure of Some Bio Compounds with Antibiotic Effect



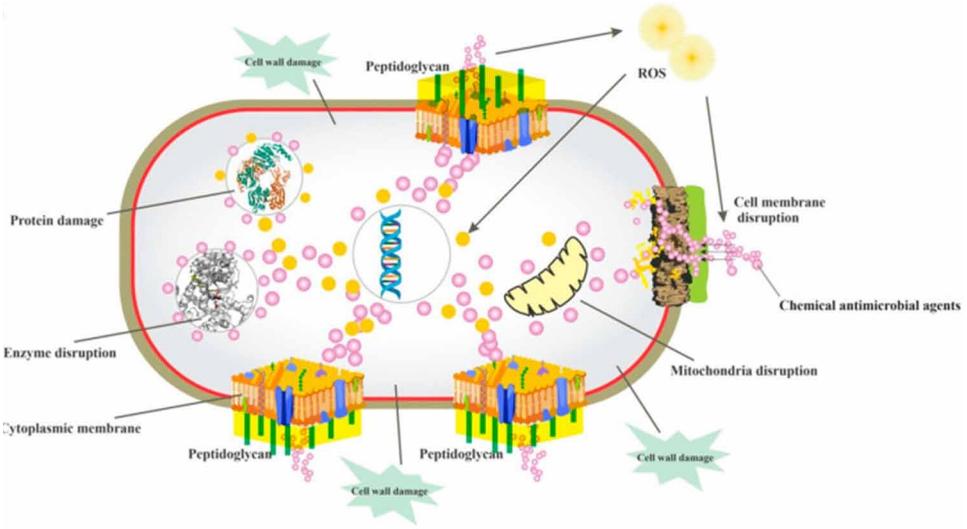
quercetin-3-rutinoside and quercetin, also inhibited the growth of *Asaia bogorensis,* and *A. lannensis,* as Antolak *et al*. (2018) showed. *In vitro* efficacy of the association *M. piperita* essential oil with different classic antibiotics was evaluated against numerous Gram-positive and Gram-negative bacteria, using

Figure 2. Schematic Presentation of the Main Mechanisms of Antibacterial Action of Plants (Pancu et al., 2021)



checkerboard microdilution method. The synergistic effect of *M. piperita* essential oil with gentamicin inhibited the growth of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Associations of ampicillin with *M. piperita* essential oil showed also a strong synergistic effect on *Escherichia coli* and *Bacillus subtili*s strains (Rosato *et al*., 2018). The peppermint essential oil act as antibacterial effects with a mechanism of disrupting the structure of membranes, which leads to the loss of integrity and elevated cell permeabilization, and inhibition of RNA and protein synthesis due to the hydroxyl group in phenol compounds (Tafrihi *et al*., 2021).

Figure 3. Antimicrobial mechanisms of herbal agents
(Parham et al., 2020)



Salvia officinalis L.

Plant Description

Sage is a perennial plant from the Lamiaceae family, native to the Mediterranean region, but has been naturalized worldwide, especially in Europe and North America. In the traditional European medicine, *S. officinalis* is used to treat excessive sweating and hot flashes associated with menopause, as a remedy for digestive disorders accompanied by bloating, cramps, to improve memory and age-related cognitive impairment, or inflammation of the throat and skin.

Biological Activities

Several studies support the antimicrobial effects of *S. officinalis. S. officinalis* essential oil has a significant inhibitory effect against Gram-positive and Gram-negative bacteria such as *Aeromonas hydrophila, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia, Pseudomonas morgani, Salmonella species, Shigella sonei* and *Bacillus subtilis*. Data from the literature report values of minimum inhibitory concentration (MIC) between 12.5-225 µg/mL (Golestani *et al*., 2015, Ghorbani *et al.*, 2017, Santos *et al.*, 2017). The antibacterial potential of *S. officinalis* essential oil can be attributed to the high content of monoterpenes such as thujone, camphor, 1,8-cineole, α- and β-pinene, compounds active against a wide range of microorganisms, including Gram-positive and Gram negative. Thujone, camphor, 1,8-cineole, and carvacrol have been shown to have antibacterial effects against *Aeromonas hydrophila, Aeromonas sobria, B. mega therium, B. subtilis, B. cereus,* and *Klebsiella oxytoca* (Hamidpour *et al*., 2014; Fournomiti *et al.*, 2015). However, to explain the biological activity of sage oil, the synergistic effects of its constituents must be taken into account. *In vitro* antibacterial activity tests have shown that Gram-positive bacteria are more sensitive to sage essential oils than Gram-negative bacteria, which can be attributed to cell membrane structure (Nikaido & Vaara, 1985; Nostro *et al*., 2000). Recent studies have investigated the antibacterial potential of ethanolic extracts of *Salvia officinalis* leaves and reported a MIC of 62.5 and 300 µg/mL, respectively, against *Streptococcus pyogenes* and *Staphylococcus aures*. Another *in vitro* study showed that aqueous sage extract caused significant antibacterial activity against *Bacillus mycoides*, *Bacillus subtilis*, *Enterobacter cloacae* and *Proteus sp*. (Hamidpour *et al*., 2007). The main constituents responsible for the antibacterial activity of these extracts are rosmarinic acid, quercetin, ellagic acid, chlorogenic acid (Wijesundara and Rupasinghe, 2019; Ghorbani & Esmaeilizadeh, 2017). The antibacterial profile of *S. officinalis* was also studied by Oliveira *et al*. (2019), by testing the glycolic extract against clinical isolates with S*treptococcus mutans, Staphylococcus aureus, S. epidermidis*. The authors concluded that at a concentration of 50 mg / mL, this extract completely eliminates strains without toxic effects. Horiuchi *et al.* (2007) reported that the crude leaf extract of *S. officinalis* exerts antimicrobial activity against MDR bacteria, such as vancomycin-resistant enterococci, penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus*. The effective antibacterial compounds have been identified as ursolic acid and oleanolic acid, and the minimum inhibitory concentration (MIC) was 4 µg/mL for ursolic acid and 8 µg/mL for oleanolic acid. The two pentacyclic triterpene compounds also showed bactericidal activity against vancomycin-resistant enterococci at concentrations twice as high as MIC. No compounds showed antibacterial activity against tested Gram-negative bacteria (*E. coli, P. aeruginosa, S. marcescens*). Carnosic acid and its derivative carnosol (picrosalvin), two other

antibacterial compounds isolated from *S. officinalis* leaves, potentiate the effects of aminoglycosides on methicillin-resistant *S. aureus* (Horiuchi *et al*., 2007, Pavić *et al.*, 2019).

Thymus vulgaris L.

Plant Description

T. vulgaris L. or thyme, also known as "garden thyme," is an aromatic, perennial plant belonging to the *Lamiaceae* family. *Thymus vulgaris*, presents several chemovarieties: *T. vulgaris geranoliferum, T. vulgaris linaloliferum, T. vulgaris mircenoliferum* and *T. vulgaris terpenoliferum*, chemovarieties rich in monoterpenic alcohols; *T. vulgaris cineoliferum,* rich in monoterpenic oxides; *T. vulgaris thujanoliferum*, rich in monoterpenic hydrocarbons; *T. vulgaris carvacroliferum* and *T. vulgaris thymoliferum* rich in monoterpenic phenols (carvacrol and thymol). The aerial parts of the plant are traditionally used for bronchitis, whooping cough, flu, fermentative colitis, biliary colic, intestinal parasitosis, buccopharyngeal infections, myalgia, for various skin problems such as acne, dermatitis, insect bites.

Biological Activities

The various extracts of *T. vulgaris* L. (ethanol and water) and essential oils obtained from the plant were evaluated and reported as having broad-spectrum antibacterial action (chemotypes *thymoliferum, geranioliferum* and *linanoliferum*) and of choice on *Chlamydia* (*T. vulgaris thujanoliferum*). In a study, Hammad *et al.*, (2007) investigated the effect of aqueous extracts of *T. vulgaris* on the growth and adhesion of *Streptococcus mutans* to human oral epithelial cells. The 20% aqueous extract resulted in a significant inhibition of bacterial cell growth (96%), and a greater reduction in bacterial cell adhesion to oral epithelial cells compared to the effect of chlorhexidine digluconate. The ethanolic extract obtained from the aerial parts of *Thymus vulgaris* showed MIC between 3.12-6.25 mg/µL on the bacteria *Escherichia coli*, *Klebsiella pneumoniae, Staphylococcus aureus, Listeria monocytogenes, Yersinia enterocolitica, Enterococcus faecalis* (Gnat *et al*.). Another *in vivo* study in an animal model showed that methanolic extract of *T. vulgaris* L. is effective against methicillin-resistant *S. aureus* (MRSA); MIC was 2.53 and 3.83 CFU / mL, for bacteria isolated from the throat and lungs, respectively (Arshad *et al*., 2017).

Thyme essential oil develops antimicrobial activity on both Gram-positive and Gram-negative bacteria. *In vitro* studies have shown strong antibacterial action of *Thymus vulgaris* oil on *S. pyogenes, S. mutans, A. actinomycetemcomitans* and *P. gingivalis*. In the case of *Salmonella typhirium,* the essential oil of *T. vulgaris* L. showed a MIC of 25.5 mm (Fadil *et al*., 2018), and the biofilm of *Salmonella enteritidis* was inhibited at MIC/MBC of 0.156/0.315 µL/mL (Čabarkapa *et al.*, 2019). Thyme essential oil has also been shown to act against methicillin resistant *S. aureus* (MIC 18.50 µg/mL) (Tohidpour *et al*., 2010). The most intense antibacterial activity of this essential oil was observed against blaCTX-M-1-producing *E. coli* S22 / 12 and ESBL-producing *Klebsiella pneumoniae* S34 / 15 with a MIC of 2.87 µg / mL. In addition, *E. coli* producing blaCTX-M-1 was more sensitive than *E. coli* producing blaSHV-12 (Benameur *et al*., 2019). Even thyme essential oil vapors are highly effective against respiratory tract pathogens (Inouye *et al.*, 2006). The antimicrobial properties are mainly attributed to monoterpenic phenols, thymol and carvacrol, strong anti-infective agents, but also to geraniol, linalool alcohols. Experimental studies have suggested that a higher content of phenolic terpene compounds results in a higher inhibitory activity (Fani *et al.*, 2017). In addition to thymol and carvacrol, phenolic acids, polyphenolic carboxylic acids

(chlorogenic acid, rosmarinic acid) and tannins are also compounds responsible for the antibacterial potential of thyme. Regarding the antibacterial activity, thyme essential oil develops a higher inhibitory activity compared to that of aqueous extracts, ethanol and even some antibiotics (Fadil *et al.*, 2018).

Rosmarinus officinalis L.

Plant Description

Rosemary belongs to the *Lamiaceae* family. It is an aromatic shrub, evergreen, native to the Mediterranean region, naturalized worldwide. It is traditionally used to relieve muscle pain, to support the immune and circulatory system, to maintain the health of the digestive system due to its choleretic, stomachic, antispasmodic, antioxidant, antibacterial properties. The species has several chemovars, of which the most used are: *R. officinalis camphoriferum*, *R. officinalis* L. *cineoliferum*, *R. officinalis* L. *verbenoniferum*. *R. officinalis camphoriferum* has a stronger antibacterial action than the other two.

Biological Activities

Numerous studies have shown the effectiveness of the essential oil obtained from the aerial parts of the species and its components on pathogens. Recently, Stojiljkovic *et al.* (2018) investigated the antibacterial action of rosemary volatile oil on Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus, Bacillus cereus, B. subtilis, B. pumilis, Pseudomonas aeruginosa, Salmonella poona, E. coli*. The test results showed a higher antibacterial activity of the essential oil against Gram-positive bacteria (MIC 0.20-0.48 mg/mL^{-1}) than against Gram-negative bacteria (MIC 1.16-1.72 mg / mL^{-1}). *In vitro* studies done by the micro-dilution method against *S. aureus* and *S. epidermidis* strains showed inhibitory and bactericidal effects of this oil, the minimum inhibitory concentration (MIC) varying between 1.25 and 2.5 µl ml^{-1} for *S. aureus* and between 0.312 and 0.625 µl ml^{-1} for *S. epidermidis*. The minimum bactericidal concentration (MBC) against the two bacteria reached higher values and was of the order of 5.0 and 2.5 µl/mL, respectively. In addition, the tested oil resulted in an inhibition of *S. epidermidis* biofilm of over 57% at a concentration of 25 µL/ mL (Jardak *et al*., 2017). Experimentally, it has been shown that *R. officinalis* essential oil shows improved antibacterial effects in combination with other oils, such as clove essential oil (*Syzygium aromaticum*), results observed in testing on pathogens such as S. *epidermidis, S. aureus, B. subtilis, E. coli, P. vulgaris,* and *P. aeruginosa* (Fu *et al*., 2007). The antibacterial activity of rosemary volatile oil is mainly imprinted with 1.8 cineole, camphor, limonene, α-pinene, Z-linalool oxide and borneol, terpene compounds known for their anti-infective profile (Bozin *et al.,* 2007). According to Manilal *et al.*, (2021), the hydroalcoholic extract of *R. officinalis* leaves reduced the growth in different degrees of some clinical isolates of MDR. The best inhibitory values (MIC) were recorded against *S. aureus, Enterococcus sp.* and *Salmonella sp*. and ranged from 4.103 to 32.103 µg/mL. Inhibitory activity on *S. pyogenes, Proteus sp*. and *Campylobacter sp*., proved to be small. In a comparative analysis, Moreno *et al*. (2006) evaluated the antibacterial efficacy of a methanolic extract with a content of 30% carnosic acid, 16% carnosol and 5% rosmarinic acid and an aqueous extract containing only 15% rosmarinic acid. They concluded that the antimicrobial activity of rosemary extracts is associated with the content of phenolic compounds; rosmarinic acid and carnosic acid being the main bioactive compounds with antimicrobial action. Furthermore, the study suggested that the methanolic extract was effective against both Gram-positive bacteria (MIC between 2 and 15

μg/mL) and Gram-negative bacteria (MIC between 2 and 60 μg / mL) as opposed to the aqueous extract which showed low activity, the study indicating a synergistic action of the compounds in the methanolic extract. The antibacterial potential of rosemary was also observed in a clinical study, which evaluated the efficacy of a mouthwash containing hydroalcoholic extracts of *Zingiber officinale, R. officinalis* and *Calendula officinalis*, concluding that the preparation was effective in patients with gingivitis, and the effectiveness was comparable to chlorhexidine mouthwash. (Mahyari *et al.,* 2016).

Melaleuca alternifolia (Maiden & Betche) Cheel

Plant Description

Tea tree is a shrub or tree from *Myrtaceae* family, native to Australia. It has been used by Australians in traditional medicine as antiseptic and anti-inflammatory to treat various infections for almost 100 years. Tea tree essential oil contains terpinene-4-ol, α-terpinene, γ-terpinene, α-terpineol, 1,8-cineole, ρ-cymene, terpinolene, and limonene, as major constituents and exerts a strong antioxidant and antibacterial activity, as confirmed by many *in vitro* tests.

Biological Activities

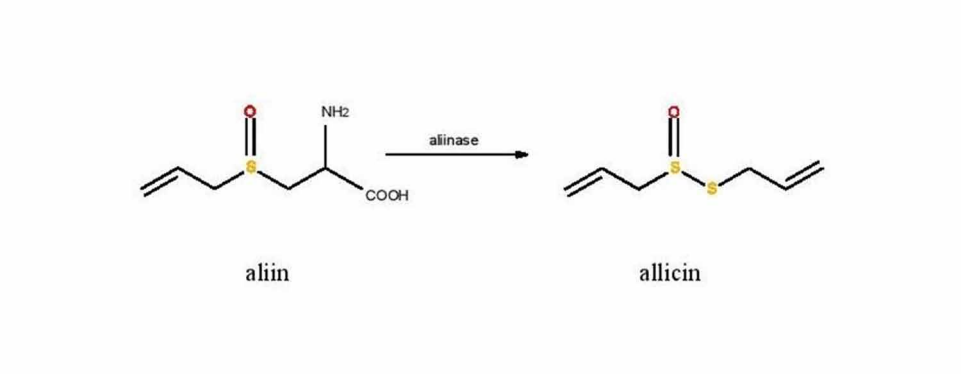
Zhang *et al*. (2018) noticed that the essential oil of *M. alternifolia* displayed significant antimicrobial activity on Gram-positive and Gram-negative bacteria as *Staphylococcus aureus, Pseudomonas aeruginosa, P. italicum, P. digitatum* and *Escherichia coli* strains, with a MIC raging between 2 and 24 mg/mL. According to these authors, " the hydrophobic terpenes from the essential oil interact with the membrane lipids of the pathogenic microorganisms, which affect the permeability of the membrane, leading to a deficit in the production of cellular energy caused by the decrease in ATP generation, and cellular lyses due to leakage or coagulation of the cytoplasm" (Zhang *et al*., 2018). Ferrini *et al.* (2006) found that from terpien-4-ol, from the tea tree essential oil has an efficient antibacterial activity on *Staphylococcus aureus*, even for the antibiotic resistant strains. Another *in vitro* study performed by Kokina *et al*. (2019) showed the inhibition of tea tree essential oil on the bacterial growth of *Staphylococcus aureus* and *Salmonella* Typhimurium with a MIC of 10, respectively > 10 μg/mL.

Allium sativum L.

Plant Description

Garlic is an alimentary plant belonging to *Amaryllidaceae* family. Garlic has been used in traditional medicine since ancient times. It contains phenolic, polysaccharides and thiosulfinates as major components. Garlic also contains flavonoids, saponins, aminoacids, enzymes, vitamins A, B and C, and minerals (Parham *et al*., 2020). The alliinase enzyme transforms alliin to allicin which is one of the main components of garlic (Figure 17.4). Allicin is the thiosulfinate responsible for the antimicrobial activity of this medicinal plant, having both bacteriostatic and bactericidal effects.

Figure 4. The conversion of Alliin to Allicin in Garlic



Biological Activities

Many *in vitro* studies demonstrated the antibacterial effect of garlic extracts against Gram positive and Gram-negative bacteria, including those resistant to antibiotics, such as *Staphylococcus aureus, Pseudomonas, Klebsiella, Salmonella typhi, Enterococcus faecalis, Proteus,* and *Escherichia coli* (Bakri & Douglas, 2005; Yadav *et al*., 2015; Rawat, 2015; Petropoulos *et al*., 2018; Ismail *et al*., 2020; Parham *et al*., 2020; Pancu *et al*., 2021). The antibacterial effect of *Allium sativum* was proved using different extracts: crude extracts, powder, various solvents extracts, and also the biocompounds isolated from this plant. The aqueous and alcoholic extract of garlic contain organosulfur compounds as *S*-allyl cysteine, *S*-methyl cysteine, and *S*-allylmercapto-L-cysteine (Bhatwalkar *et al*., 2021). Avato *et al*. (2000) revealed that garlic distilled oil with diallyl disulfide and diallyl trisulfide is effective on different Gram-positive and negative bacteria cultures (*S. aureus*, *B. subtilis, P. aeruginosa* and *E. coli*). The mechanism of action consists in binding to the thiol groups of enzymes in bacteria, which leads to the microbial inactivation.

Arctostaphylos uva-ursi L.

Plant Description

Arctostaphylos uva-ursi L., from the *Ericaceae* family, is an evergreen shrub that grows in the northern hemisphere, abounds in the Arctic regions, and only at high altitudes in the temperate and Mediterranean area. For a long time, the leaves of this plant have been used in traditional medicine to combat and treat urinary tract diseases, like infections such as cystitis or urethritis, as a diuretic and anti-inflammatory agent for various diseases of the urogenital tract.

Biological Activities

Many studies have shown the effectiveness of bearberry leaf extracts in urinary tract infections through antibacterial activity and the ability to reduce recurrences in people at risk of contracting these infections. Moskalenko (1986) showed that the ethanolic extract of *Uvae ursi folium* has strong bacteriostatic activity on *Bacillus subtilis, Escherichia coli, Shigella sonnei* and *Shigella flexneri*. In another study,

Anukk *et al.,* (1999) reported that aqueous bearberry leaf extracts show remarkable bacteriostatic activity on *H. pylori* strains. This activity could be related to the ability of the aqueous extract to modulate the hydrophobicity of the cell surface and to increase the aggregation of cells, an effect determined by the high content of tannins. Various extracts (aqueous, ethanolic and ethyl acetate) from *A. uva - ursi* leaves were tested on strains of *Enterococcus faecalis* and strains of *Escherichia coli,* etiological agents of urinary tract infections. *In vitro* results concluded that the aqueous extract has a stronger antibacterial effect on *E. coli* (MIC 0.625-5 mg/mL) compared to ethanolic and ethyl acetate extracts (MIC 10 mg/mL), while the effect on *Enterococcus faecalis* was similar for the three types of extracts. It should be noted that the extracts showed stronger antibacterial activity against Gram-positive strains (Vučić *et al*., 2013). Arbutin metabolites (hydroquinone, hydroquinone glucuronide, hydroquinone sulfate) are considered to be the compounds responsible for the urinary antiseptic activity of the plant. They exert antimicrobial action on a wide range of pathogens involved in the infectious pathology of the urinary tract, *E. coli, Proteus vulgaris, Acinetobacter baumanii, Ataphylococcus aures, Bacillus subtilis, Enterococcus faecalis, Neisseria gonorrhoeae* (Ștefănescu *et al.*, 2019). Although it was initially thought that hydroquinone could be released from arbutin only by alkalizing urine, more recent research challenges this hypothesis. Hydroquinone deconjugation is now thought to be catalyzed by intracellular enzymes present in the bacterial cytoplasm. Alkalization of urine does not appear to be a prerequisite for the release of hydroquinone from arbutin (Quintus *et al*., 2005). The pharmacology of the whole plant has also been shown to be different from that of arbutin alone. Crude plant extracts are more medically effective than isolated arbutin (Asensio *et al.*, 2020). In addition, *A. uva - ursi* extracts have been shown to be helpful in increasing the susceptibility of antibiotic-resistant bacteria such as beta-lactams. A group of Japanese researchers studied the effect of corilagin, a polyphenolic compound isolated from *A. uva - ursi,* against methicillin-resistant *Staphylococcus aureus*. Corilagin reduced the minimum inhibitory concentration of oxacillin and other beta-lactam antibiotics by 100 to 2000 times, the effect of corilagin and oxacillin being synergistic (Shimizu *et al.*, 2001).

Glycyrrhiza glabra L.

Plant Description

Liquorice is an herbaceous perennial plant from *Fabaceae* family, native to Southern Europe, Western Asia, and North Africa. This specie has an important therapeutical value, being used since centuries for a wide range of pharmacological properties, including anti-inflammatory, antibacterial, antiviral, antiulcer, and antidiabetic activities. Many biological compounds have been found in this medicinal plant: simple glucides, polysaccharides, pectins, gums, resins, coumarins, tannins, oestrogens, phytosterols, amino acids, proteins, minerals, vitamins (B_1, B_2, B_3, B_5, C and E), Triterpenoid saponins (glycyrrhizin, responsible for the sweet taste), and flavonoids (liquiritigenin and isoliquiritigenin) are the most important constituents (Pastorino *et al*., 2018).

Biological Activities

Gupta *et al*., 2008 and Wang *et al*., 2015 showed the antimicrobial action of *G. glabra* extract on Gram-positive and Gram-negative bacteria cultures, as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Bacillus subtilis* (Gupta *et al*., 2008; Wang *et al*., 2015). Responsible for the

antibacterial effect are the secondary metabolites from plant: flavonoids, saponins, and alkaloids, (hispaglabridin A, hispaglabridin B, glabridin, glabrol glabrene, 40-methylglabridin, and 3-hydroxyglabrol). Authors noticed that "the mechanism behind this could be the decrease of bacterial gene expression, the inhibition of bacterial growth, and the reduction of bacterial toxin production" (Gupta *et al*., 2008; Wang *et al*., 2015). Liquorice may inactivate methicillin resistant *Staphylococcus aureus* (MRSA) through a mechanism that involves lowering the expression of the key virulence genes of MRSA and can also have an inhibitory action on *Streptococcus pyogenes*, as Fukai *et al*. (2002) has shown. Gupta *et al*. (2008) also demonstrated the antibacterial action of *G. glabra* against *Mycobacterium tuberculosis*, glabridin beeing the responsible compound for this activity. Asha *et al*. (2013) noticed that the flavonoid glabridin from liquorice exherts activity against *H. pylori*, by inhibition of the protein synthesis, DNA gyrase, and dihydrofolate reductase. Another *in vitro* study showed that the liquorice polysaccharides also present activity against *Porphyromonas gingivalis* adhesion (Chinsembu, 2016).

Hypericum perforatum L.

Plant Description

Hypericum perforatum L. (*Hypericaceae*) is a perennial plant native to Asia and Europe, known as St. John's wort. In traditional medicine it is used as a remedy against skin lesions, sunburn, for diseases of the gallbladder, depression, dysentery, and diarrhea. More recent studies have focused on the antidepressant effects and antimicrobial activity of St. John's wort extracts and their components.

Biological Activities

Avato *et al*., 2004 tested the microbiological activity of various extracts against Gram-positive bacteria (*Bacillus subtilis*, *B. cereus*, *Staphylococcus aureus*, *Enterococcus*) as well as Gram-negative (*Pseudomonas aeruginosa*, *Acinetobacter calcoaceticu*s, *A. baumani*i). It turned out that the pharmacological activity depends on the type of extract and the solvent used to obtain it. The most active were chloroform and ethanolic extracts against *B. subtilis* and *B. cereus* with a MIC value of 12.5 µg / mL. In addition, the ethanolic extract significantly inhibited all other Gram-positive bacteria tested, showing a MIC of 12.5 µg/mL, except for *E. faecalis* (MIC = 50 µg/ mL). The active compounds responsible for the antibacterial activity have been shown to be hypericin, hyperforin and its stable ammonium dicyclohexyl salt. In a study on the antibacterial activity of an extract in petroleum ether from aerial parts of *H. perforatu*m, Reichling *et al*. (2001) reported that hyperforin is the major active compound against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* strains, with a MIC of 1 µg / mL. Various extracts and isolated fractions of aerial parts of *Hypericum perforatum* have been tested for anti-*Helicobacte*r activity. In such a study, the butanolic fraction showed anti-*Helicobacter pylori* activity at MIC values between 15.6 and 31.2 µg/mL (Saddiqe *et a*l., 2010).

CONCLUSION

As most of the studies that proved the antibacterial effect of plant extracts have been performed on *in vitro* cultures of bacteria, *in vivo* studies and clinical trials are required to be realized in future. The

Table 1. Antibacterial Activity of Some Plant Extracts

Plant	Extract	Tested bacteria /MIC	Responsible antibacterial compounds	Authors
Mentha x *piperita*	• essential oil • methanolic extract • ethanolic extract	• *Staphylococcus aureus*, *Streptococcus pneumoniae*, *E. coli*, *P. aeruginosa*, *Salmonella typhi* and *Klebsiella pneumoniae* / 0.5–8 µg/mL • *Salmonella enterica/4.12*µg/mL • *S. aureus, P. aeruginosa, E. coli,* and *K. pneumoniae* • *Salmonella typhius*, *B. subtilis*, *S. aureus*,, *Staphylococcus epidermititis*, *P.aeruginosa,* and *Klebsiella pneumonia* • *Helicobacter pylori* /25–100 µg/mL • *Asaia bogorensis,* and *A. lannensis*	• mentol, menthone • carvone, menthol, and menthone • menthol, menthone, camphane, menthofuran • carvone, carveol, menthone, menthol • phenolic compounds • gallic, chlorogenic, neochlorogenic, p-coumaric, ferulic, rosmarinic acids, epicatechin, quercetin-3-rutinoside and quercetin	• Abolfazl *et al*., 2014 • Valková *et al*., 2021 • Osanloo *et al.*, 2020 • Saba & Anwar, 2018 • Mahady *et al*., 2005 • Antolak *et al*., 2018
Salvia officinalis	• essential oil • ethanolic extracts	• *Aeromonashydrophila, Aero monassobria, E. coli, Klebsiella oxytoca, Pseudomonas morgani, Salmonella anatum, Klebsiella pneumonia, Salmonella enteritidis, Salmonella typhi* and *Shigella sonaan/* 12.5-225 µg / mL • *Strptococcus puogenes* and *Staphylococcus aures*/ 62.5 and 300 µg / mL	• thujone, 1,8-cineole and camphor • rosmarinic acid, quercetin, ellagic acid, chlorogenic acid	• Ghorbani *et al.,* 2017; Santos *et al.*; 2017; Sonboli, *et al.*, 2006 • Wijesundara and Rupasinghe, 2019
Thymus vulgaris	• essential oil • methanolic extract • ethanolic extract	• *S pyogenes, S mutans, P. gingivalis* and *A actinomycetemcomitans* • *Salmonella enteritidis/* 0.156 µl / ml • *S. aureus* (MRSA)/ 2.53 and 3.83 CFU (log10) / ml • *Escherichia coli, Klebsiella pneumoniae, Yersinia enterocolitica, Staphylococcus aureus, Listeria monocytogenes, Enterococcus faecalis /* 3.12-6.25 mg / µL	• thymol, carvacrol, p-cymene • thymol, carvacrol, p-cymene • phenolic and polyphenolcarboxylic acids • phenolic and polyphenolcarboxylic acids	• Fani *et al.*, 2017 • Čabarkapa *et al*., 2019 • Arshad *et al*., 2017 • Gnat *et al*., 2017
Rosmarinus officinalis	• essential oil •hydroalcoholic extract • ethanol extracts	• *Staphylococcus aureus, Bacillus cereus, Bacillus pumilis Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Salmonella poona*, • *Staphylococcus aureus* (ATCC 9144)/ 1.25 to 2.5 µl ml^{-1} • *Staphylococcus epidermidis/* 0.312 to 0.625 µl ml^{-1} • *S. aureus, Salmonella sp* and *Enterococcus sp* / 4.103 to 32.103 µg / mL. • *Staphylococcus saprophyticus, S. epidermidis, P. aeruginosa,* and *Enterococcus faecalis /*70–350 µg / mL	• Limonene, camphor, eucalyptol, α-pinene, Z-linalool oxide and borneol • carnosic acid, carnosol, rosmarinic acid • carnosic acid, carnosol, rosmarinic acid	• Stojiljkovic *et al.*,2018; Bozin *et al.* 2007 • Jardak *et al*., 2017 • Manilal *et al*., 2021 • Petrolini *et al.*, 2013
Melaleuca alternifolia	• essential oil	• *E. coli, S. aureus,, P. italicum Wehmer, P. aeruginosa and P. digitatum Sacc. /* 2 - 24 mg/mL • *Staphylococcus aureus* and *Salmonella* Typhimurium/ 10, and > 10 µg/mL	• terpinene-4-ol, γ-terpinene, and α-terpinene • valencene, trans-cadina-1(6),4-diene, aromadendrene	• Zhang *et al*., 2018 • Kokina *et al*., 2019
Allium sativum	• aqueous extract • ethanolic extract • distilled oil	• *Neisseria gonorrhoeae, S. aureus*, and *Enterococcus faecalis* • *M. tuberculosis, S. aureus, S. mutans, and P. aeruginosa* • *S. aureus*, *Bacillus subtilis, E. col,i* and *P. aeruginosa*	• *S*-allyl cysteine, *S*-allylmercapto-L-cysteine, and *S*-methyl cysteine • allicin • diallyl and allyl methyl sulfides	• Bhatwalkar *et al*., 2021 • Bhatwalkar *et al*., 2021 • Avato *et al*., 2011
Arctostaphylos uva-ursi	• ethanolic extract • aqueous extract	• *Bacillus subtilis, Escherichia coli, Helicobacter pylori, Shigella sonnei* and *Shigella flexner* • *E.coli* /MIC 0.625-5 mg / mL)	• arbutin metabolites (hydroquinone, hydroquinone glucuronide, hydroquinone sulfate)	• Moskalenko, 1986 • Vučić *et al.,* 2013
Glycyrrhiza glabra	• ethanolic extract	• *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* • *S. aureus* (MRSA) • *Helicobacter pylori* • *Mycobacterium tuberculosis*	• glycyrrhizin, 18β-glycyrrhetinic acid, liquiritigenin, licochalcone A, licochalcone E, and glabridin • flavonoids • vestitol, licoricone, 1-methoxyphaseollidin and gancaonol glycyrrhizin, 18β-glycyrrhetinic acid, liquiritigenin, licochalcone A, licochalcone E, and glabridin • glabardin	• Wang *et al*., 2015 • Fukai *et al*., 2002 • Fukai *et al*., 2002 • Gupta *et al*., 2008
Hypericum perforatum	• chloroform extract •ethanolic extracts • butanol extract in	• *B. subtilis* and *B. cereus* / 12.5 µg / ml • *Bacillus subtilis*, *B. cereus*, *Staphylococcus aureus*, 25923, *Enterococcus faecalis* / 12.5 - 50 µg / ml µg / ml •*Helicobacter pylori* / 15.6 - 31.2 µg / ml	• hypericin, hyperforin, ammonium dicyclohexyl salt	• Avato *et al*., 2004 • Reichling *et al.*, 2001

mechanisms of antimicrobial action of biological compounds from plants must be completely elucidated, and additionally, their toxicity on humans should be evaluated.

This chapter summarizes the significance of the antibacterial activity of some plant extracts due to their constituents, as demonstrated by the scientific studies. Biological compounds from plants can be used as an alternative to chemical, synthetic antibiotics, or used complementary, synergistic for better therapeutically results.

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Chapter 5
Dietary Components Consisting of Bioactive Molecules in the Prevention of Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases and cognitive disorders originating from these are among the age-related diseases with the highest mortality rates. Our lifestyle, especially our eating habits, has an effect on neuronal survival. New data shows that improving dietary habits provides successful results in the prevention or treatment of diseases. The effective role of bioactive components on neuronal survival helps develop new therapeutic approaches. In this chapter, the potential benefits of bioactive foods and particularly flavonoids that can be used to reduce the incidence of neurodegenerative diseases will be examined.

INTRODUCTION

Neurodegenerative diseases are identified by the progressive loss of selectively sensitive neuron populations resulting from metabolic or toxic disorders. Especially with aging, the development of neurodegenerative disorders accelerates. Up to date, more than 600 nervous system disorders that affect the normal function of the brain, spine, or the nerves have been described. The structures, electrophysiological and neurochemical properties of the brain, spinal cord and nerves can be affected. Any condition that leads to neurodegeneration may result in a disorder that affects cognitive and motor functions. Neurodegenerative diseases can have a number of clinical manifestations which are largely dependent on the pathological

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mechanisms occurring in various parts of the brain. Chronic degeneration of the brain may develop due to changes at molecular and cellular level. However, these mechanisms have not been fully elucidated. Among these mechanisms, the most well-known are; neuroinflammation, protein aggregation due to failure of protein degradation pathways including the ubiquitin-proteasome system, chronic oxidative stress, mitochondrial dysfunction, impaired axonal transport, changes in RNA metabolism, and failure in triggering of apoptosis (Friese *et al.,* 2014; Goodfellow *et al.,* 2020).

Cognitive dysfunctions, motor disabilities and progressive synaptic loss are common in many neurodegenerative diseases, causing ravaging changes for patients. Recent studies have shown that having atherosclerosis, hypertension, obesity and type 2 diabetes are among the most common risk factors for Parkinson's disease (PD), Alzheimer's Disease (AD) and Hungtinton's disease (HD)-related dementia (Farooqui, 2018). Since we do not know the pathogenesis of most of these diseases, environmental factors become even more important. Regulating some environmental conditions may help prevent or delay neurodegeneration. Neurodegeneration can be directly affected by our lifestyle. We can assume that one of the most important changes is the regulation of eating habits. Memory loss and other cognitive problems have been associated with reduced intake of certain dietary nutrients, particularly in older individuals. Even though aging is a natural process and is influenced by a number of variables such as stress and lifestyle, environment and genetics, the process of aging can be controlled by diet. By maintaining neuron health, a quality life and a healthy mind and body can be achieved. Understanding the mechanisms of risk factors causing neurodegeneration has led to development of new therapeutic strategies. Recent data have demonstrated the significance of natural food-based approaches in disease management. In modern era, researchers have published more publications focusing on benefits of health-related products and how food products can boost and sustain a healthier life.

Bioactive compounds which are abundantly found in nature are mainly the secondary metabolites found in plants and in addition to their nutritional value, they have other functions such as stimulation of growth for their metabolism and protection against biotic and abiotic stress (Nogueira *et al*., 2020). Since bioactive components have many biological functions, including but not limited to their anticoagulant, antihypertensive, antiproliferative, antioxidative, antithrombotic, antidiabetic, anti-inflammatory and cardioprotective effects, they can also play important roles in the prevention of many diseases such as cancer, neurodegeneration and cardiovascular diseases (Acevedo-Fani *et al*., 2020; Stacchiotti & Corsetti, 2020). Realizing the positive effects of bioactive components on health has spawned new therapeutic approaches that play an important role in reducing neurodegeneration. Studies have shown that using supplements that contain polyphenolic compounds found in fruits and vegetables provides beneficial effects such as preventing and reversing the harmful effects of aging on neuronal function and behavior. This protection is likely due to the antioxidant and anti-inflammatory properties of fruits and vegetables (Rice-Evans & Miller, 1996).

This chapter aims to present a comprehensive review of the potential benefits of dietary bioactive compounds to reduce the incidence of neurodegenerative diseases.

BACKGROUND

Neurological diseases such as AD, PD, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS) are chronic conditions, which significantly hinder the patient's quality of life and significantly impose on families and governments. The factors that cause neurodegeneration are quite complex and comprise

very different mechanisms. Pathomechanism of neurodegeneration seems to be affected by more than one factor as toxic reactions such as glutamatergic neurotoxicity, inflammation, depletion of endogenous antioxidants, increases in nitric oxide and iron levels, and reduced activity of ubiquitin-proteasome pathway cause neuronal cell death. In addition to all these disrupted mechanisms, the rapidly increasing lifespan of humans also increase neurodegeneration. As we know, aging is a major risk factor for many diseases characterized by apoptosis, cell cycle, cell senescence, and changes in expression of mitochondrial genes. Other causes include gender, low education level, endocrine disorders, smoking, exposure to chemical substances, stroke, diabetes, vitamin deficiencies, depression, hypertension, head trauma, infection, tumors, immune and metabolic conditions (Ulatowski & Manor, 2015; Zhang & Butterfield, 2017; Di Meo *et al*., 2019). Among all these complex mechanisms, neuroinflammation, oxidative stress and excess accumulation of proteins are common pathological features of neurodegenerative diseases *(*Uddin *et al*., 2020).

Chronic neuroinflammation and oxidative stress are two key pathological factors enmeshed in neurodegenerative diseases and aging of the brain, and one can be the consequence of the other. The never-ending cycle between oxidative stress, neuroinflammation and neurodegeneration can initiate chronic and progressive neurodegeneration. Reactive oxygen species (ROS) act as physiological signaling molecules and have significant roles in many biological processes such as post-translational processing of proteins, cell growth, synthesis of molecules, immune response, and metabolic processes. However, if the levels of ROS increase more than required, they can oxidize nucleic acids, lipids and proteins, thereby contributing to aging and the development of various diseases, including cancer, diabetes, obesity, atherosclerosis, cardiovascular and neurodegenerative diseases (Angelova & Abramov, 2018). The major factors contributing to the formation of oxidative stress are endoplasmic reticulum (ER) stress and Ca^{2+} entry into the cell that which develops as a result of mitochondrial dysfunction. Oxidative metabolism of neurotransmitters, increased activity of oxidase enzymes, mitochondrial dysfunction, increased demand for oxygen consumption and high energy result in excess levels of ROS production in the brain. Extreme levels of reactive oxygen species/reactive nitrogen species (ROS/RNS) may cause oxidation/nitrosylation of nucleic acids, lipids and proteins. Activation of apoptotic processes and excitotoxicity can lead to loss of neurons (Di Meo *et al.,* 2016; Naeem *et al*., 2021). Excessive ROS/RNS production or decreased activity of enzymatic and non-enzymatic antioxidants may cause damage. Both enzymatic antioxidants (e.g. glutathione peroxidase, catalase, and superoxide dismutase (SOD)) and non-enzymatic antioxidants (e.g. β-carotene, phenolic compounds, vitamin C, vitamin E, flavonoids) are essential for maintaining redox balance in the brain. Inadequate antioxidant defense may also end up with excessive ROS levels. Therefore, when the antioxidant defense system is suppressed by increased levels of ROS, oxidative stress can augment brain dysfunction and chronic neurodegeneration, which may then again increase oxidative stress (Milisav *et al*., 2018; Mittler, 2017). Therefore, a complex balance between pro- and antioxidant reactions is required to keep normal functions of neurons.

A large body of evidence has suggested that the accumulation of damage due to oxidative stress can occur during normal aging, which in turn can cause significant impairments in cognitive function (Uddin *et al.*, 2020). The best-established risk factor for neurodegenerative diseases is aging, which is closely related to oxidative stress. Analysis of postmortem human brain specimens have revealed that the expression levels of genes encoding learning, memory and synaptic transmission have decreased after age 45, which has been linked to damage in gene promoters due to increased oxidative stress (Perry *et al*., 2002; Lu *et al*., 2004).

Inflammation is a cellular and immune response to an attack aimed at restoring normal tissue structure and function. When the metabolism is unable to prevent the damage caused by ROS at the desired level, oxidative damage occurs. Astrocytes and microglia are major cells that take part in the fight against inflammation in the brain. They are in charge of producing inflammatory and immune reaction associated molecules While reactive astrocyte products generally have a tendency to protect the neurons, inflammatory cytokines and other microglia-derived factors cause neurotoxicity (Sharman *et al*., 2019). Since the neurodegenerative mechanisms and the integration of these mechanisms with each other are not fully clarified, living conditions and dietary habits become more important. Studies have linked diet to the risk of developing neurodegenerative diseases. It has been shown that having an unhealthy diet (such as a diet high in calories or saturated fat) increases oxidative stress and inflammation (Erro *et al*., 2018; Ramirez-Salazar *et al*., 2021). Research has shown that in diabetes mellitus, a metabolic disease that is closely related to nutrition, brain aging may be related to abnormal insulin levels and may affect cognitive abilities. Studies have shown that hyperinsulinemia may affect the pathophysiology of AD and exacerbate clinical symptoms and, is responsible for a decrease in memory performance (Bourdel-Marchasson *et al*., 2010; Cholerton *et al*., 2011; Sanz *et al*., 2012). Since this relationship is also related to the cerebrovascular system, vascular dementia may occur (Strachan *et al*., 2011). Despite being under the effect of genetic factors, insulin resistance largely develops as a result of lifestyle. It seems that cognitive and physical brain damage are inevitable due to neuronal degeneration that will occur after increased resistance to insulin. One can suggest that dietary modifications are one of the most important factors that need to be regulated in order to prevent the emergence of such disorders. Understanding such relationships not only contributes to understand the mechanisms, but also helps explore new therapeutic approaches.

Neuroprotection is important as well as neuroregeneration. It seems that delaying or preventing neuronal survival is more practical and easier than neuroregeneration. Since the relationship between the aforementioned causes and neurodegeneration has not been fully elucidated, we must take into account the role of environmental factors. Among these factors, eating habits, which seriously affect human life, come first. The number of dietary studies on neuronal survival is quite limited. Therefore, from the socio-economic point of view, it is necessary to enlighten these mechanisms and to increase and accelerate studies on components of food that can prevent neuronal degeneration.

DIFFERENT DIETS FOR COGNITIVE AND PHYSICAL SURVIVAL OF THE BRAIN

Of all living things, humans eat the most diverse foods as we are the only organisms that can source, process and consume many different foods. Since the beginning of modern times, our diet has changed. The transition to a diet with more refined carbohydrates and increased saturated fat has given rise many metabolic disorders and health problems. Lifestyle and dietary habits have been often directly related to hypertension, diabetes, and neuronal survival. Diets can directly affect the physiology of the circulatory system, thereby triggering the development of these diseases (Ravera *et al*., 2016). Therefore, the diet, which is no longer considered as just nutrition, becomes even more important for human health.

Research has shown that diet can modulate apoptosis, detoxification and gene response. Prolongation of life expectancy also brings neurodegeneration over. Studies aiming to delay or stop neurodegeneration have shown that certain amino acids and various other compounds of plant and animal origin should be present in the diet (Virmani *et al*., 2013). Since oxidative stress plays a role in the pathogenesis of

neurodegeneration, it can inhibit the ROS activity that causes oxidative stress by increasing the activity of endogenous antioxidants. Oxidative stress can directly initiate neuronal cell death. Excitotoxicity, Ca^{2+} overload and mitochondrial disorders activate apoptotic processes (Uddin *et al*., 2020). As a result, some cognitive and physical diseases related to neuronal death may develop. Recent studies show that inflammation due to neurodegenerative disease is under direct influence of nutrition. A number of studies are being conducted to explore the possible links between diet and disease risk, as well as the effect of diet on disease progression. Intake of the various dietary factors such as -3 fatty acid, antioxidants, chemical compounds and calorie can increase or decrease the oxidative damage and affect the inflammatory response (DeLegge & Smoke, 2008; El Soury *et al*., 2021). At this point, we come across foods that contain some health-promoting compounds, which can be used against neurodegeneration and the decrease in cognitive abilities that occur afterwards. The most common terms for these functional foods are medicinal foods, bioactive foods, and therapeutic foods (Nagai & Inoue, 2004; Chakrabarti *et al.,* 2018).

Due to the presence of pharmacologically active compounds, the prophylactic benefits of edible plants are under investigation for their potential use as new drugs. A food product with a therapeutic effect or value that can be used to treat or prevent diseases is called a medicinal food. They can also exert physiological effects on functions of a certain tissue and can work to reduce the risk of certain diseases. Medicinal plants can be described as edible plants with therapeutic effects in traditional, ethno and biomedicine. The use of these foods have been strictly regulated as they may cause toxicity in humans, and their data sheets for test results and records must be traceable and accessible at all times. The safety, efficacy and shelf life of these food products must be carefully and precisely documented (Ramalingum & Mahomoodally, 2014; Selvakumarasamy *et al*., 2021). A relatively new category of food which offers health benefits after consuming the product that goes beyond basic nutrition is functional foods. There are three general classes of functional foods, depending on their preparation method: modified foods, conventional foods, and synthetic food ingredients.

Traditional foods naturally contain bioactive components with health benefits and are whole, unmodified foods such as fruits and vegetables, fish, dairy products and cereals (Chauhan *et al.,* 2013). Modified foods are normal foods enriched with functional food compounds such as plant extracts (Lafarga *et al.,* 2020). Synthetic food components are foods prepared by producing the functional components in the laboratory.

Nutrients can be defined as structural and functional components or substances in foods that provide energy to the body. In general, foods can be classified as: Calorie providing nutrients, nutrients that meet the basic growth and maintenance needs such as fatty acids, and non-essential nutrients which are necessary to maintain health such as plant-based foods. Bioactive foods and bioactive compounds obtained from natural plant-based sources have been drawing more attention lately and they have emerged as natural antioxidants which can be used to reduce the risk of many diseases, including neurodegeneration. Bioactive food components can meet basic needs for nutrition and can be taken in diet or as supplements. Bioactive components should be taken regularly in sufficient quantities and should be a part of the standard diet in order to achieve the desired benefit.

BIOACTIVE DIETARY COMPONENTS IN THE PREVENTION OF NEURODEGENERATIVE DISEASES

As life expectancy increases, the frequency of diseases caused by neuronal degeneration increases. Due to this increase, it is an urgent need to help people have a healthy body and mind, maintain the quality of life, and treat and finally hinder age-related diseases. Bioactive compounds are biologically active compounds obtained from edible sources that can be used as additives in the food and other industries. These active compounds, which are also called phytochemicals and found in vegetables, fruits, grains, legumes and tea, play a role in the prevention of many diseases. In recent years, the number of studies inquiring the effects of these active compounds on neuronal survival has increased. These studies aim to protect the quality of life and decrease financial problems by preventing the development of neurodegenerative diseases.

Low levels of ROS production help maintain physiological functions, including proliferation, defense of the body and signal transduction (Singh-Mallah *et al*., 2019). The brain is especially susceptible to oxidative stress and neuroinflammation due to the huge numbers of neurotransmitters, neurotransmitter receptors, ROS-sensitive polyunsaturated fatty acids, and restricted potential of neuronal regeneration. The chronic neurodegenerative process can be triggered by the vicious circle between oxidative stress, neuroinflammation, and neurodegeneration. As a result, inhibiting the generation of ROS can diminish neuroinflammation and vice versa. Generally speaking, since bioactive foods have strong antioxidant, anti-inflammatory and immunomodulatory properties, they are protective against oxidative stress, which enables them to prevent development of neurodegenerative diseases (Weaver, 2014). Recently, bioactive molecules have gained more attention, especially in the prevention/delay of cognitive disorders that develop with age.

Vitamins, carotenoids, and polyphenols are the most important bioactive components present in fruits and vegetables, and they have the potential to support a healthy metabolism and prevent diseases (Akhtar *et al*., 2015). The next sections will go through the synthesis and biological consequences of these bioactive chemicals, as well as their functions in the prevention of neurodegenerative diseases.

Polyphenols

Oxidative stress and impaired metabolism of certain neurotransmitters such as glutamate, GABA, acetylcholine, dopamine or serotonin play a decisive role in the pathogenesis of neurodegenerative diseases. It has been shown that biologically active plant polyphenols have a positive effect on the function of the central nervous system (CNS) through the modulation of metabolism and the effect of some neurotransmitters (Rebas *et al*., 2020). Considering that the polyphenols are non-toxic, we can assume that they can be alternatives to the conventional treatment methods of neurodegenerative diseases as well as support.

Neuronal degeneration can occur as a result of excessive production of ROS and proinflammatory mediators (Uttara *et al*., 2009; Bhullar & Rupasinghe, 2013). One of the powerful options to prevent or slow down this formation is to take components with antioxidant and anti-inflammatory properties. Regular intake of fruits rich in polyphenols can help delay the development of neurodegenerative diseases by using their strong antioxidant and anti-inflammatory properties (Youdim & Joseph, 2001; Hamaguchi *et al*., 2006; Pandey & Rizvi, 2009). Polyphenols are the most abundant and widely dispersed bioactive molecules. Polyphenols have been shown to have a wide range of biological activities, and numerous studies have emphasized the positive effects of phenolic compounds, indicating their potential as thera-

peutic tools for a number of disorders (Fraga *et al*., 2019). Some of the polyphenols have neuroprotective effects and they exert their effect by making changes in some signaling pathways and neurotransmission (Rahimifard *et a*l., 2017). Polyphenols specifically bind to the TrkB receptor, which phosphorylates the CREB protein by activating the Ras/ERK 1/2, PI3K/Akt, BDNF and PL-Cy pathways. The transcription of *Bcl-2* and antioxidant genes that regulate cell survival is thus increased by CREB, which inhibits neurodegeneration. Polyphenols also boost neuroprotective efficacy by activating the Keap-Nrf2-ARE signaling pathway (Uddin *et al*., 2020).

The Blood Brain Barrier (BBB) acts as a barrier to ensure the stability of the physiological environment of the brain tissues and to prevent harmful agents from damaging the CNS. The BBB consists of endothelial cells that form the inner surface of the capillaries and the tight connections between these cells (Xie *et al*., 2019). Gap junction proteins are found in astrocytes, pericytes, and endothelial cells interconnected via the extracellular matrix, and they work in collaboration in order to regulate the movement of ions, molecules, and cells between the blood and brain to create a good environment for proper neuronal function (Pervin *et al*., 2019). *In vivo* and *in vitro* research have documented that some flavonoids can pass the BBB (Faria *et al*., 2014).

According to the nature of the carbon skeleton, polyphenols are classified into four main groups: Phenolic acids, flavonoids, stilbenes and lignans (Scalbert & Williamson, 2000).

Flavonoids

Flavonoids are a group of non-nutrient polyphenolic phytochemicals, which naturally occur as bioactive compounds and are found in plants. Depending on the oxidation state of the pyran ring, flavonoids can be classified into six subgroups: anthocyanins, flavanols, flavonols, flavanones, flavones, and isoflavones (Bhagwat *et al*., 2014). Anthocyanins include compounds such as petunidin, pelargonidin, peonidin, malvidin, delphinidin and cyanidin, while genistein and daidzein are classified as isoflavones. These chemicals are categorized based on their chemical structures and biological activities. Genistein and daidzein of isoflavones are mainly found in legumes. Resveratrol, especially found in the skin of red grape, is a non-steroidal polyphenolic compound and is considered a phytoestrogen.

Microglial cells, a major type of brain cell, are glial neurons that can migrate in case of oxidative stress and inflammation. However, these microglial cells can create cytokines and inflammatory chemicals like superoxide and nitric oxide in cases of severe oxidative or inflammatory damage. While flavonoids can activate antioxidant genes such as *SOD* and *GPX* through their antioxidant properties (Zaidun *et al*., 2018), NF-kB, IL1, IL6 cytokines can inhibit *BCL2* (Nam, 2006).In addition, they decrease caspase activity, and they can activate neurogenesis by activating CREB, BDNF, ERK1/2 (Muhammad *et al*., 2019). Since flavonoids are active in many signaling pathways in the central nervous system, and can pass through the BBB, they have important effects on neuronal survival.

Anthocyanins

Anthocyanins are classified under a large group of compounds known as flavonoids. Anthocyanin molecules are commonly associated with fruits, although they are also found in roots, legumes, vegetables and grains. In particular, blueberries, blackberries and mulberries are rich sources of anthocyanins (McGhie & Walton, 2007). Bioavailability and absorption studies have shown that anthocyanins begin to show their mechanism of action immediately after dietary intake. Various studies have shown that oral micro-

flora provides beta glucosidase activity, which is also present in the human intestinal epithelium. These findings suggest that oral microflora, saliva, and the entire oral epithelium may contribute to formation of bioactive aglycon from major anthocyanins. Therefore, starting from the oral cavity, anthocyanins interact with enzymes with similar functions and structures throughout the digestive tract. Anthocyanins metabolized by the oral microbiota are also rapidly absorbed in the stomach, but the maximum absorption site is the intestine (Passamonti *et al*., 2003; Charron *et al*., 2007; Charron *et al*., 2009). The bioavailability of anthocyanins is affected by the intensive metabolism of bacteria in the colon. Because it is well known that probiotic bacteria can have a variety of health benefits, the good effects shown after consuming anthocyanins may be attributed in part to regulation of gut microbiota. The metabolization of anthocyanins by gut microbiata produces short-chain fatty acids. This situation both causes a decrease in pH and creates a suitable environment for the proliferation of probiotic bacteria (Zhu *et al*., 2018). In this way, anthocyanins have a potential role in modulation of gut microbiota and neuroinflammation. It is believed that the gut microbiota can positively alter the modulation of the production of toxic proteins such as tau and amyloid, thereby providing massive benefits for public health (Zilli & Zilli, 2021). It has been shown that a diet rich in anthocyanin decreases *TCK-1* expression in the hippocampus by increasing Pseudoflavonifractor and Sporobacter genera. In addition, it has decreased lippolysaccharide (LPS) production in fecal microbiota and increased the production of neuroprotective metabolites by changing tryptophan metabolism (Marques *et al*., 2018). Many experimental models which prove the benefits of dietary anthocyanins have shown that anthocyanins are effective in the prevention of various types of cancer, diabetes, cardiovascular and neurodegenerative diseases by possibly affecting a number of cell signaling cascades, triggering anti-inflammatory response and controlling gene expression (Hui *et al.*, 2010; Takikawa *et al*., 2010; Chen *et al*., 2015).

The accumulation of inflammatory factors act quite importantly in the development of neurodegenerative diseases. In a mice model of Alzheimer's disease (AD), anthocyanins can effectively cause a decrease in expression levels of inflammatory factors, thus Ap1-42 peptide can positively affect the development of inflammation. Furthermore, anthocyanins can reduce the expression of the AD-activated nuclear factor kappa B. (NF-KB) (Poulose *et al*., 2012). On top of that, anthocyanin administered for 14 days has prevented LPS-induced oxidative stress, neurodegeneration and neuroinflammation in the cortex of adult mice (Khan *et al.,* 2016). About the effect of anthocyanin on cognitive function, it has been documented that following sixteen weeks of daily supplementation, blood oxygen level-dependent activation was increased in the left middle frontal gyrus, left pre-central gyrus, and left inferior parietal lobe in participants supplemented with anthocyanin-rich blueberry. These data show the increased neural response during working memory challange with cognitive decline in older adults treated with blueberry (Boespflug *et al*., 2018). Overproduction of ROS and proinflammatory mediators is often associated with neuronal degeneration. Therefore, the cognitive protective effects of anthocyanins are largely attributed to their antioxidant and anti-inflammatory properties.

It is clear that anthocyanins positively affect cognitive and motor functions with their regulatory effects on neuronal survival. It has been shown that anthocyanins can easily pass the BBB where they stimulate the communication between cells and neuronal regeneration (Manolescu *et al*., 2019) and can be localized in some parts of the brain, affecting signaling pathways at the molecular level, and thus inhibiting or slowing down the formation of neurodegeneration (Spencer, 2010; Rendeiro *et al.*, 2015). Therefore, consumption of purple fruits should be a part of a healthy lifestyle.

Flavanols

Flavanols contain compounds such as catechin, gallocatechin, epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (Ottaviani *et al*., 2020). Since flavanols directly interact with neurons at the molecular level by generating signaling that increases connections between neurons, antioxidants have been demonstrated to promote brain performance and memory at all ages, as well as enhance and protect brains in older adults (Cox *et al*., 2015). Amyloid-β (Aβ) formation is observed from the early stages of many neurological diseases, including AD. Studies have shown that flavanols have a protective effect against neurodegeneration, so early use can lessen the risk of developing the disease (Mandel *et al*., 2008). Catechins, which is a subgroup flavanols, are found in many fruits and vegetables such as tea, cocoa, grapes. Green tea, which contains catechins, has been shown to regulate cognitive abilities and protect against aging of the brain (Pervin *et al.,* 2019). Catechin can be consisted of four different structures: (+) catechin, (-) catechin, (+) epicatechin, and (-) epicatechin. The (-) epiform (-) epigallocatechin gallate (EGCG) is the most abundant catechin in green tea (Unno & Nakamura, 2021). EGCG is a flavanol with very strong antioxidant properties. EGCG can inhibit the aggregation of amyloidogenic proteins such as Aβ monomers, α-syn, and calcitonin, which are important in many neurological diseases (Bieschke *et al*., 2010). It has been demonstrated that following administration of 300 mg EGCG, the activities of alpha, beta, and theta brain waves increased in EEG activity (Scholey *et al*., 2012). This result shows that EGCG can prevent stress-related oxidation, regulate cognition, and has a relaxing and refreshing effect. Catechins in green tea is effective in the development of long-term memory (Pervin *et al*., 2019), and spatial working memory (Unno & Nakamura, 2021), and thus catechins can be beneficial for developing new cognition-enhancing drugs.

Flavanones

Among the flavanones, naringenin, hesperidin, naringin, eriodicytol are the ones which have been widely studied for their effects on neuroprotection, apoptosis, and synaptic dysfunction. Naringenin, a flavanone, is commonly found in fruits, especially citrus fruits, bergamot, tomatoes, and lemons. In addition to their anti-inflammatory, immunomodulatory, antiproliferative and antioxidant effects, they are good neuroprotectors, and therefore many studies have investigated their function in neuronal survival (Dobrzynska *et al*., 2020; Bhia *et al*., 2021). One study has shown that administration of naringenin to propofol-exposed mice suppressed neurodegeneration, prevented apoptosis, and enhanced learning memory response (Zou *et al*., 2020). However, since the bioavailability of naringenin is low and its dissolution is difficult, some researchers have opted for nanocoating of naringenin. In a study on ischemic experimental animals, naringenin was coated with chitosan and administered intranasally. In cerebral ischemic rats, neurobehavioral activity improved and infarct volume decreased. These results have shown that naringeninin exhibits a strong neuroprotective effect against oxidative stress (Ahmad *et al*., 2020). In a comparable study using the SH-SY5Y cellular model of Parkinson's disease, naringenin was found to have improved neuroprotective and antioxidant properties against 6-OHDA-induced neurotoxicity (Md *et al.*, 2019).

Another compound found in flavanones and closely related to neuronal survival is hesperidin. It is found in citrus fruits such as orange and grapefruit. In a study with streptozotocin (STZ)-treated mice, hesperidin has exerted a protective effect against STZ-induced memory impairment and neuronal apoptosis (Hajizadeh Moghaddam *et al*., 2020). Another study has demonstrated the neuroprotective effect

of hesperedin against neuroinflammation, neurodegeneration, synaptic dysfunction, LPS-induced glial activation and memory problems in mice (Muhammad *et al*., 2019). Eriodictyol, another flavonoid compound, has been shown to alleviate memory impairment and Aβ accumulation and Tau phosphorylation by activating the Nrf2/HO-1 signaling pathway via vitamin D receptor (VDR) mediated mechanism (Li *et al*., 2022). Its effect on suppressing the neurodegeneration, especially in AD, suggests that it can be used for a new treatment approach.

Flavones

Among the most important flavones are luteolin, chrysin, apigenin and tangeritin. The effects of these flavones on neuronal survival have been documented by both in *in vivo* and *in vitro* studies. It has been shown that luteolin, one of the flavones, has decreased the levels of tumor necrosis factor-α (TNF-α), prostaglandin E2 (PGE2), IL-1β and nitric oxide (NO), and resulted in an antioxidant, anti-inflammatory and neuroprotective phenotype by affecting the microglial transcriptome (Kempuraj *et a*l., 2021). *In vivo* experiments have shown that apigenin can alleviate hypoxic-ischemic brain injury by down-regulating apoptosis via the PI3K/Akt/Nrf2 signaling pathway (Wilms, 2005). Similarly, in the presence of CD40 ligation, luteolin and apigenin inhibited interferon-gamma-induced microglial TNF- and IL-6 production (Rezai-Zadeh *et al*., 2008). In a study conducted with rats with traumatic brain injury (TBI), chrysin has been shown to improve vestibular dysfunction, reduce memory-related problems and anxiety/depression. It has also been observed that chrysin has anti-inflammatory and anti-apoptotic effects (Rashno *et al*., 2020). According to a similar study, fisetin administration lowered neuronal cell death and apoptosis, elevated B-cell lymphoma 2 (Bcl-2), decreased Bcl-2-related X protein (Bax) and caspase-3 expression after TBI, resulting in a neuroprotective effect (Zhang *et al*., 2018). Tangeretin, a flavon that is found in the peel of the citrus fruits, has antiasthmatic, antioxidant, anti-inflammatory and neuroprotective properties. One study has shown that tangeretin can be used as a therapeutic strategy against ischemic reperfusion injury, as it increases the activity of superoxide dismutase, decreases the levels of ROS and malondialdehyde, and ameliorate the injury (Wu *et al*., 2019). In addition, its neuroprotective effect has been emphasized in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Braidy *et al*., 2017).

Flavonols

Neurodegeneration associated flavonols can be classified as: kaempferol, quercetin, myricetin.It has been shown that Kaempferol acts specifically on the mitochondrial Ca^{2+} uniporter (mCU) channel and is able to cross the BBB in animals with traumatic brain injury which were treated with Kaempferol (Parent *et al*., 2020). Kaempferol has suppressed the expression of numerous pro-inflammatory proteins in brain ischemia reperfusion rat models by decreasing the phosphorylation and nuclear translocation of the transcription factor NF-KB p65 (Li *et al*., 2019).

While quercetin is abundantly found in asparagus, onions, red leaf lettuce, cherries, apples and strawberries, it is also found in many fruits and vegetables, even in low amounts. Due to its very strong antioxidant capacity, many *in vivo* and *in vitro* studies have been conducted to investigate its function in neurodegenerative diseases. Quercetin's bioavailability is low and it has a lipophilic compound (Andres *et al*., 2018). It can cross the blood-brain-barrier so that it can exert its neuroprotective effects. It has been demonstrated that the conjugated forms of isorhamnetin-3-O-glucuronide (methylquercetin-3-O-

glucuronide) and Quercetin-3-O-glucuronide accumulate in cerebral tissue after oral administration of quercetin (Babaei *et al*., 2018). Quercetin exerts a protective effect against MPP+-induced oxidative stress in dopaminergic neurons (Bournival *et al*., 2009), protect neurons against LPS-induced microglial toxicity and attenuate neurodegeneration in PD mouse models (Boyina *et al*., 2020), and improve cognitive abilities (Sriraksa *et al*., 2012). It has been reported that, in neuronal-microglial cell cultures, LPS-induced *TNF-α* and *IL-1* gene production was suppressed in glial cells, and inflammatory-induced neuronal death was reduced (Bureau *et al*., 2008). In addition, another study has suggested that administration of quercetin 40mg/kg for 16 weeks in the APPswe/PS1dE9 transgenic mouse model of AD may reduce ROS production, mitochondrial dysfunction, plaque formation, and improve cognitive deficits (Babaei *et al*., 2018). These findings suggest that quercetin acts as a pro-antioxidant in the brain and could be employed as a nutraceutical in the treatment of neurodegenerative diseases.

Myricetin is a light yellow flavonol that is commonly found in fruits and vegetables such as apple, mulberry, strawberry, spinach, aloe and carrot. Due to its strong antioxidant effects, myricetin has been shown to provide clinical benefit in the treatment of neurodegenerative diseases. Myricetin has antioxidant, anti-inflammatory and anti-tumor effects (Pluta *et al*., 2021). It has been shown that myricetin reduces infarct volume caused by cerebral ischemia and improves cerebral and mitochondrial function (Wu *et al*., 2016). One study showed that myricetin lowered endothelial permeability and inflammation in a brain cell model of oxygeneglucose deprivation and reoxygenation, and considerably contributed to BBB function via activating the eNOS/NO pathway (Zhang *et al.*, 2019). Nevertheless, quercetin and myricetin can be used efficiently to preventing DNA damage induced in lymphocyte cell lines or human lymphocytes (Wilms *et al*., 2005).

Isoflavones

Isoflavones have biological effects on neuronal systems. They are a type of phytoestrogen, naturally occurring compounds in plants that serve as the main source of protein in many soy products and standard rodent feeds. The steric structure of these molecules is comparable to that of steroidal compounds. They have the ability to bind to the human estrogen receptor (ER) and thus perform a number of estrogenic or anti-estrogenic actions (Duncan *et al*., 2003). A number of studies have focused on different isoflavones such as daidzein and genistein and their function in neuronal survival. Phytoestrogens have direct effects on androgen receptors in the brain, and they can affect neural circuit activities when combined with their ER actions. The activation of second messengers associated with plasticity in the hippocampal synapse was reduced in male mice which were fed a low phytoestrogen diet. This diet caused a significant reduction in long-term potentiation (LTP) in the ventral hippocampus, as well as reduced intermale aggressiveness, changes in territorial marking behavior, and a general disruption of social behavioral patterns (Gorzkiewicz *et al*., 2021). ER expression and localization are dynamic processes, varying according to cell type, hormonal condition, area of the brain, and neurological function. Both ERa and ERb are highly expressed in the brain and have a distribution pattern that corresponds to their roles in cognition and reproduction. Some clinical studies have revealed that changes in estrogen levels in the postmenopausal period cause negative effects on the cognitive level (Spencer *et al*., 2008; Vargas *et al*., 2016). Isoflavones can ameliorate neurological deficits and reduce brain infarct volume in rats using the ER pathway alone, as well as reduce neural death induced by oxygen-glucose deprivation plus reoxygenation (OGD/RO) and L-glutamate treatment in neuron cell lines in a dose-dependent manner (Gu *et al*., 2021). The offspring of pregnant rats fed with an isoflavone-rich diet have better learning

and memory development (Lephart *et al*., 2002), and their brains are protected against oxidative stress and neuronal apoptosis (Yan *et al*., 2019).

Genistein is a natural isoflavone compound found mainly in legumes, with antioxidant, anti-aging, anti-inflammatory, anti-senile dementia and anti-tumor effects (Jiang *et al*., 2021). Besides being an enzyme inhibitor and regulator of peroxisome proliferation, it also affects genes that control cell growth through its effects on natural killer cell function (Sarkar & Li, 2003). By revealing the mechanisms underlying its anti-inflammatory effects, it has been found that genistein can inhibit the expression of proinflammatory factors, which are induced by β-amyloid (Jiang *et al*., 2021), Additionally, genistein can activate cAMP/CREB-BDNF-TrkB-PI3/Akt signaling pathway and exert neuroprotective effects (Jiang *et al*., 2017).

Daidzein, another isoflavones, is known with its neuroprotective and neurotrophic effects. It has been shown that neurons of dorsal root ganglion can stimulate neurite outgrowth depending on Src kinase, PKCδ and ERK (Extracellular regulated kinase) signaling pathways (Yang *et al*., 2012). Nevertheless, a study on rats has shown that daidzein has reduced cell death in rat cortical neurons caused by exposure to oxygen-glucose deprivation and improved synaptic function in terms of increased synaptic vesicle recycling in nerve terminals (Hurtado *et al*., 2012). In addition, the association of daidzein with neurotensin 1 and interleukin-10 receptors, its neuroprotective properties and positive effects on cognitive processes have been documented (Alo *et al*., 2021).

Stilbenes

Resveratrol is a stilbene found in a variety of plants such as grapes, blueberries, raspberries, and peanuts. Resveratrol exerts neuroprotective effects in experimental models of Alzheimer's disease and Parkinson's disease, but is chemically unstable when exposed to high temperatures, pH changes, UV light, or certain enzymes. Due to its rapid metabolism and low bioavailability, its application in the clinic is quite limited. To overcome these restrictions, resveratrol can be carried in nanocarriers to extend the half-life and aid pass through the BBB. Reservatrol was encapsulated using a variety of nanomaterials, including liposomes, lipid and polymeric nanoparticles. To recognize their targets in the brain, some of these nanocarriers have been engineered with targeting molecules (Liu *et al*., 2020; Siddiqui *et al*., 2021). Resveratrol has been shown to protect neurons by activating ERK-induced CREB regulation, triggering the release of glial cell-derived neurotrophic factor (GDNF), BDNF and NGF, and suppressing the levels of IL-1, IL10, and NF-κB (Anastacio *et al*., 2014), and resveratrol potentially protects neurons by taking part in neuroinflammation in this way (Granzotto & Zatta, 2011; Yang *et al*., 2014). Oral treatment of resveratrol has inhibited microglia activation related to the cortical Aβ plaques formation in a mouse model of cerebral deposition, reducing the proinflammatory action of Aβ on macrophages (Capiralla *et al*., 2012). Furthermore, in an age-related mouse model of AD (SAMP8), long-term dietary resveratrol consumption was linked to decreased tau hyperphosphorylation, cognitive impairment and amyloid load, which showed the neuroprotective effect of this compound (Capiralla *et al*., 2012).

Carotenoids

A variety of organisms such as bacteria, fungi, plants and algae contain carotenoids, a family of red, orange and yellow pigments. Although carotenoids are especially found in green leafy vegetables, they are also found in eggs, corn, milk and some fish species (Bohm *et al*., 2021). As people show more

interest and increase awareness for natural foods, interest in natural colorants such as carotenoids that can be used in food industry also increases, both because they have coloring properties and they are strong antioxidants. The neuroprotective effects of dietary carotenoids, including beta-carotene, lutein, lycopene, astaxanthin and fucoxanthin, have been demonstrated by various studies (Park *et al*., 2020). Dietary carotenoids are antioxidants that work against oxidative stress with their free radical scavenging properties. Carotenoids are essential precursors for the production of retinoids such as vitamin A in humans. Carotenoids are also associated with many developmental processes. Some carotenoids have other biological activities for human health. Carotenoids have been associated with reduced incidence of various chronic diseases such as cardiovascular diseases and neurodegenerative diseases such as stroke (Bohm *et al*., 2021).

While lycopene is exclusively found in red tomato varieties and watermelon, it is also found in certain amounts in other red vegetables and fruits. Studies on the therapeutic effects of carotenoids in human diseases have received a lot of attention in recent years and due to its efficacy and safety, lycopene is among the top investigated carotenoids. It protects hippocampal neurons against apoptosis, inhibits pro-apoptotic proteins, and protects anti-apoptotic proteins (Qu *et al*., 2011). Lycopene is thought to be one of the most powerful anti-inflammatory phytochemicals, as it can lower oxidative stress *in vivo* through chain-breaking mechanisms and by donating electrons. Lycopene has been demonstrated to have modulatory effects on a variety of neurodegenerative disorders. It has been suggested that lycopene's neuroprotective effect is related to its capacity to permeate the blood-brain barrier and scavenge ROS (Ugbaja *et al*., 2021). *In vivo* and *in vitro* experiments have shown that lycopene, through the Nrf2/NF-kB signaling pathway, can reduce apoptosis and inflammation in neurons and the nervous system, eventually alleviating hypoxic ischemic brain injury, thus lycopene can be an effective alternative to other drugs (Fu *et al*., 2020). The β-(beta) carotene is one of the best-known food carotenoids and is occasionally found in certain foods along with α-carotene. The β-carotene can be detected in carrots, mangos, and apricots, while α-carotene is typically found in carrots and pumpkin. The β- carotene is the most abundant provitamin A carotenoid in foods and is a natural molecule (Stutz *et al*., 2015). It is known that β-carotene is highly absorbed in the body and metabolized in humans.

It has been shown that β-carotene has improved neural functions and cognitive performance and reduced ROS production in TBI rat model (Chen *et al*., 2019). In addition, it has been shown that β-carotene supports neural plasticity and increases cognitive abilities (Avraham *et al.*, 2019; Hira *et al*., 2019).

Lutein, a dihydroxy derivative of β -carotene, is present in a variety of yellow and orange fruits and flowers, as well as green vegetables. It has been shown that it has a neuroprotective effect especially in retinal degeneration and is important in preventing age-related macular degeneration, which is the prominent cause of blindness (Ozawa *et al*., 2012). Fucoxanthine was found to alleviate traumatic brain injury induced secondary brain injury, including brain lesion, cerebral edema, neurological deficits, and neuronal apoptosis (Zhang *et al*., 2017).

Astaxanthin, which crosses the blood brain barrier with its special structure, has been shown to reduce cognitive impairment in *in vivo* and *in vitro* models of neurodegenerative diseases (Galasso *et al*., 2018). Astaxanthin is the main form of carotenoid detected in marine animals such as salmon, shrimp, lobster and crabs, and other microorganisms. Astaxanthin has β-carotene and its antioxidant capacity 10 times higher than lutein, therefore it is referred to as super vitamin E (Higuera-Ciapara *et al*., 2006). This may be due to its molecular structure, which includes hydroxyl and keto.

Vitamins

Vitamins offer an apparent advantage to prevent neurodegenerative diseases and preserve cognitive functions. Both water- and fat-soluble vitamins significantly prevent PD and AD. The effects of the use of vitamins A, B, C, D and E in appropriate doses on neurodegeneration and cognitive processes have been shown in different studies.

Vitamin A or retinoid derivatives have been frequently advocated as treatment agents for AD and psychiatric disorders such as schizophrenia. Vitamin A, through its primary metabolite retinoic acid, has been shown to have profound effects on behavior in post-embryonic and adult life and brain physiology. One of the classic hallmarks of human aging is reduced cognitive function, which has been shown in animal models after inadequate vitamin A supplementation (Biyong *et al*., 2021).

In the nervous system, vitamins B1, B6, and B12 have diverse neurospecific activities. Due to their various biochemical effects as coenzymes, all of these are essential for the preservation of normal neurological processes (Calderon-Ospina *et al*., 2020).

It has been demonstrated that atrophy of brain regions related to cognitive functions (such as hippocampus, parahippocampal gyrus, inferior parietal lobule and cerebellum) can be slowed down after high-dose vitamin B administration (vitamin B6 20 mg, vitamin B12 0.5 mg, folic acid 0.8 mg) to elderly individuals (Douaud *et al*., 2013). Vitamin B6 is a water-soluble cofactor that participates in many functions. Individuals suffering from mild cognitive impairment have high homocysteine levels, and it has been shown that it can reduce dementia rates by bringing homocysteine levels back to normal levels (Cheng *et al*., 2016).

Insufficient vitamin B12 and folate levels are associated with brain atrophy, cognitive decline, and dementia. As a result of a 5-year study, it has been found that individuals with low plasma vitamin B12 levels had greater brain volume loss (Vogiatzoglou *et al.*, 2008). Supplementing with vitamin B12 may have a neuroprotective effect in people who have low amounts of the vitamin. Low levels of vitamin B12 in the elderly should be studied in clinical trials as a modifiable cause of brain shrinkage and cognitive impairment.

Vitamin C, commonly known as ascorbic acid, is a water-soluble vitamin found mostly in fresh vegetables and fruits. It plays an active role in metal ion metabolism, tyrosine degradation and conversion of cholesterol, carnitine, steroid hormones and neurotransmitters into bile acids (Lh & Ahluwalia, 1997; Rumsey & Levine, 1998). Vitamin C is a micronutrient for the central nervous system. It also plays a role in neurotransmitter synthesis and cognitive function (May, 2012).

Vitamin D is expressed in both the embryo and the adult brain. With its neuroprotective properties, it has a very important role in the connection of neuronal circuits, both via direct and indirect routes. It has been proposed that it is important for neuron growth, survival, and proliferation, and hence could be used to treat a variety of neurodegenerative diseases (AlJohri *et al*., 2019). Low serum levels of vitamin D have been associated with sleep disorders, multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, autism spectrum disorders, cognitive decline in patients affected by schizophrenia and elderly individuals (Bivona *et al*., 2019). Taking vitamin D daily may contribute to the preservation of cognitive abilities by preventing neurodegeneration.

Vitamin E can be found in corn, soybean, safflower, and cottonseed oil, as well as green leafy vegetables and wheat germ. One of its tasks is to act as an antioxidant and scavenger of free radicals (Uneri *et al*., 2006). Dose adjustment, on the other hand, is critical. Vitamin E at high amounts (above 3000

IU/day) is hazardous and has been linked to a variety of symptoms including gastrointestinal cramps, exhaustion, and diarrhea (Farina *et al*., 2017).

Oxygen free radicals are very reactive because they contain oxygen atoms with unpaired electrons. They can harm proteins, DNA, and cell membranes unless they are immediately 'quenched' by antioxidants. They are waste products of the body's metabolism and can also be caused by radiation exposure. Unless they are quickly 'quenched' by antioxidants, they can damage the cell membrane, DNA and proteins. They are the by-products of the body's metabolism and can also be produced by exposure to radiation.

CONCLUSION

Neurodegenerative risk factors are directly affected by changes in eating habits, lifestyle, physiological, and environmental factors. Fruits and vegetables have long been renowned for their health advantages. In addition, studies on the bioactive components of fruits and vegetables, as well as their physiological and metabolic objectives, have become more popular. The importance of studies on these areas has increased since it was recognized that bioactive components can be employed in the prevention and treatment of certain diseases. Changing the lifestyle in a positive way and consuming better and healthier foods that contain bioactive molecules on a regular basis can help protect our neurons and avoid the development of neurodegenerative diseases.

We believe that more detailed and comprehensive research is required to enlighten the effects of bioactive components in foods and to find the proper levels for the treatment of all diseases. If we want to help people in social and financial context, we should start taking preventive steps as soon as possible before the disease develops. To conclude, the government and social media should urge people consume bioactive food components in their regular diet.

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Chapter 6
Gut Effect on Phytochemicals

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ABSTRACT

The gut microbiota play an important role for host nutritional, physiological, immunological functions like food digestion, vitamin production, protection of gut integrity, regulation of host immunity, and disease pathogenesis. Dietary phytochemicals are important factors to shape and change the human gut microbiota composition in diversity and abundance context. On the other hand, the microbial community of the gut provides a broad range of enzymes to host which are different from its own resources. This enables human gut microbiota to affect and direct the biosynthesis and metabolism of many bioactive compounds. Bioavailability of phytochemicals is important to benefit from health conferring effects of these compounds. Most of the phytochemicals are not absorbed well by the small intestine and pass through to the gut then gut microbiota acts on the compounds to form different metabolites. Therefore, elucidating the role of human gut microbiota on phytochemical metabolism is essential. This chapter discusses the studies reporting the gut microbial effect on different phytochemicals.

INTRODUCTION

Human gut microbiota is known as a complex ecosystem which includes a wide variety of microorganisms. The microbial content of GI tract can be variable, it consists of approximately 10^{14} microbial cells which was estimated as 10-fold more that of human cells in an adult (Goel *et al.,* 2014). Nowadays, this ratio is accepted as 1:1 (microbial cells to human cells) (Kho & Lal, 2018) Moreover, the human microbiota is suggested to possess over 100 times more genomic content compared to the human genome even if it makes up a relatively small amount of the human body composition (Thursby & Juge, 2017). Nearly 99% of human microbiota consists of bacterial species and the rest (1%) refers to archaea, viruses and prokaryotes. The microbiota plays an important role for host nutritional, physiological, immunological functions like food digestion, vitamin production, protection of gut integrity, regulation of host immunity and disease pathogenesis (Thursby & Juge, 2017; Xu *et al.,* 2013). An adult's microbiota composition tends to remain stable but it can show fluctuations under certain conditions. For instance, acute diarrhoeal diseases, dysfunction of immune system or antibiotic intake, age and diet can modulate the gut

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microbiota composition (Xu *et al.,* 2013). Diet is an important factor shaping the microbiota composition and it is known there is a mutual relationship between human gut microbiota and diet. While diet show a strong impact on the intestinal microbial composition, the microbiota also affects nutritional value of the foods in the diet (Illiano *et al.,* 2020).

Gut microbiota is well known for its role in fermentation of non-digestable dietary residues such as carbohydrates and endogenous mucus. The microbioal community in the human gut provides a broad range of different enyzmes to the host which are different from its own resources. This potential enables biotransformation of various compounds including phytochemicals by gut microbiota and strongly affect the bioavailability of phytochemicals (Guarner & Malagelada, 2003; Illiano *et al.,* 2020).

The bioavailability of phytochemicals depends on several sequential steps. It includes the availability for absorption, metabolism, tissue distribution, and bioactivity of the compounds. The bioactivity is measured by the biological activity of components on specific organs or tissues (Fernández-García *et al.,* 2009). However to show bioactivity, the compounds should be bioavailable in first place. The release and solubility of these bioactive compounds during digestion determines further uptake and absorption. Most of the phytochemicals are not absorbed by small intestine and pass through to the gut then gut microbiota interplays its role to transform the compounds into their metabolites. Moreover, phytochemicals can also modulate composition of gut microbiota. Therefore, it is important to understand the interaction with gut microbiota to enable health promoting effects of the phytochemicals (Ozdal *et al.,* 2016).

GUT EFFECT ON PHYTOCHEMICALS

There are various types of phytochemicals such as phenolic acids, flavonoids, stilbenes, ellagitannins, proanthocyanidins, vitamins, peptides and glucosinolates. Gut microbiota can take role in sythesis of vitamins (notably vitamin K and B group vitamins) or metabolise these phytochemicals to form metabolites (Rowland *et al.,* 2018). For instance, five *Bifidobacteria* species are related with hydrolysis of soymilk isoflavones (Tsangalis *et al.,* 2002) and gut bacterial species belonging to the genera *Bifidobacterium* and *Lactobacillus* were reported to be involved in phenolic acid metabolism in the gut (Couteau *et al.,* 2001). In some cases, the hydrolysis reactions might result in the formation of more bioactive compounds than the parent compounds (Lampe & Chang, 2007). Moreover, there are inter-individual differences in metabolism of these phytochemicals due to gut microbiota profile (Lampe & Chang, 2007; Liu *et al.,* 2020). As a result, it is important to understand the metabolism of phytochemicals by human gut microbiota to maximize health benefits. Here, biotransformation of different phytochemicals by gut microbiota are discussed.

Phenolic Acids

Phenolic acids are divided two main groups as benzoic acid and cinnamic acids. They are found in many foods including coffee, tea, cocoa, fruits, vegetables and cereals (Di Lorenzo *et al.,* 2021). The essential role of gut microbiota on bioavailability of phenolic acids was suggested in many studies (Kempf *et al.,* 2010; Lara-Guzmán *et al.,* 2016).

In vitro studies can be performed as metabolism of phenolic acids by community based fecal microbiota or by pure cultures. A study isolated and identified 6 bacterial strains capable of degrading chlorogenic acid using a chlorogenic acid-based enrichment method. These bacteria were identified through 16S

rRNA sequencing as *Escherichia coli* (three isolates), *Bifidobacterium lactis* and *Lactobacillus gasseri* (two strains). Chlorogenic acid degradation was reported to be dependant on cinnamoyl esterase activity of the bacteria and mainly intracellular. Degradation of chlorogenic acid by these bacteria occured through hydrolysis to caffeic and quinic acids, and no further caffeic acid metabolites were detected (Couteau *et al.*, 2001). A study reported time and concentration dependant degradation of chlorogenic acid (caffeoyl-quinic acid) by a fecal microbiota from healthy volunteers. The main degradation product of chlorogenic acid was 3-(3-hydroxyphenyl)-propionic acid *(*Rechner *et al.,* 2004). Tomas-Barberan et al. (2014) also investigated chlorogenic acid degradation by human gut microbiota in vitro (fecal slurries from healthy volunteers) and reported the same main product (3-(3-hydroxyphenyl)-propionic acid). The study found that degradation of chlorogenic acid is possible through hydrogenation, dexydroxyation and ester hydrolyisi reactions which can take place in different order dependant on the human volunteer. The study also examined addition of *Bifidobacterium animalis*, which can degrade chlorogenic acid, to cultures but this did not result in modification of chlorogenic acid degradation.

Stalmach et al. investigated chlorogenic acid absorption by comparing human volunteers with an ileostomy and healthy individuals with a functioning colon. The results showed that approximately one-third of ingested chlorogenic acids in foods are absorbed and entered the bloodstream from the small intestine while remaining two-thirds reaches the gut in healthy volunteers. The study concluded that chlorogenic acid absorption occurred in both the intestine and the gut but it occured mainly in the gut (Stalmach *et al.,* 2010). A later study emphasized the importance of gut microbita and three important time points were reported for bioavailability of chlorogenic acid from coffee. These include absoption in the stomach and the small intestine (early; 1-2 h after ingestion), absorption in the gut (intermediate; 4-8 h after ingestion, late; 8h after ingestion)(Lara-Guzmán *et al.*, 2016). Ferulic acid is one of the main phenolic acids found in the foods and ferulic acid esterases cleaves the ester bond in plant cell wall polysaccharides and phenolic acids. On the other hand xylanases act on arabinoxylan to form ferulic acids. The studies showed that these two enzymes work synergistically to form ferulic acid from arabinoxylan (Vardakou *et al.,* 2007).

A study by Vitaglione *et al.* (2015) investigated the excretion profile of phenolics from whole grain (WG) wheat in overweight/obese subjects. The study provided 97 mg/day of ferulic acid to study group via whole grain wheat diet. The study showed that there is an increased dihydroferulic acid concentration in serum thanks to WG consumption. It is known that dihydroferulic acid can be formed from ferulic acid or chlorogenic acid. The study suggested that ferulic acid from WG wheat was biotransformed by gut microbiota and resulted in dihydroferulic acid formation. As Bacteroidetes and Bifidobacteriales showed a low abundance in overweight/obese subjects, the study proposed that fermentation of WG polysaccharides was mostly performed by Firmicutes.

A randomized controlled trial (12 healthy male subjects) aimed to evaluate the matrix effect of raw flesh or juice of 'Ataulfo' mangos on bioavailability of phenolic acids. Blood (6h after consumption) and urine samples (24 h after consumption) were collected from the subjects. Blood was collected for six hours after consumption, and urine for 24 h. g Chlorogenic, vanillic, ferulic, sinapic, gallic, and p-coumaric acids were detected in the urine. The study also reported pyrogallol presence in the urine which is a product of gut microbial metabolism. Pyrogallol was not detected in mango samples, it was suggested that it is formed from polymeric gallic acid through decarboxylation in the gut (Quirós-Sauceda *et al.,* 2017).

A randomized controlled trial by Schär et al. (2018) showed that the oat-bran intake resulted in excretion of different phenolics including vanillic acid, 4- and 3-hydroxyhippuric acids, and sulfate-conjugates of benzoic and ferulic acids. The oat bran used in the study consisted of mainly bound fractions of

Table 1. Studies Reporting the Effect of Certain Microorganisms or Community based Gut Microbiota on Phenolic acid Metabolism

Study Details	Phenolic acids & (Source if reported)	Microorganisms	Reference
In vitro fermentation studies	Chlorogenic acid (caffeoyl-quinic acid)	*Escherichia coli, Bifidobacterium lactis* and *Lactobacillus gasseri* strains	Couteau *et al.,* (2001)
	Chlorogenic acid	Community based human gut microbiota	Rechner *et al.,* (2004; Tomas-Barberan *et al.,* (2014)
Human feeding studies	Caffeic acid, Ferulic acid and p-coumaric acid conjugates (in coffee)	Not determined, colonic fermentation in gut suggested	Stalmach *et al.,* (2010)
	Chlorogenic acids (in coffee)		Lara-Guzmán *et al.,* (2016)
	Coffee	Not determined, colonic fermentation in gut suggested (inter-individual variation due to gut microbiota composition)	(Kerimi *et al.,* (2020)
In vitro fermentations using human colon model	Water-unextractable arabinoxylan fraction	Not determined, xylanase and ferulic acid esterase from human gut	Vardakou *et al.,* (2007)
A placebo-controlled, parallel-group randomized human trial	Whole-grain wheat	Not determined, colonic fermentation in gut suggested (by Firmicutes)	Vitaglione *et al.,* (2015)
Randomized crossover pilot clinical trial	Gallic, chlorogenic, p-coumaric, vanillic, sinapic, protocatechuic, ferulic, gentisic, and caffeic acids (from raw flesh and juice of 'Ataulfo' mango)	Not determined, colonic fermentation in gut suggested	Quirós-Sauceda *et al.,* (2017)
Non-blinded, randomized, controlled clinical trial	Phenolic acids, (oat bran porridge)	Not determined, colonic fermentation in gut suggested	Schär *et al.,* (2018)

phenolic acids. However, it was reported that excretion of phenolics occured within 8 h of intake. The study suggested a quick release of bound phenolics by microbial fermentation.

Some of the studies reporting the influence of gut microbiota on bioavailability of phenolic acids are listed in the Table 19.1. In brief, many studies report or suggest the effect of community based microbiota on phenolics but only a few succeed to adress the responsible microorganism at family or genus level.

A recent human intervention study emphasized the importance of gut microbiota on metabolism of coffee phenolic acids and reported inter-individual variation effects. The study showed that chlorogenic acid was transformed into dihydroferulic acid, dihydrocafeic acid and vanillic acid by microbiota and the metabolites of this biotransformation exhibit higher inter- and intra-individual variation than the ferulic acid conjugates. This variability was reported due to host specific gut microbiota composition, polymorphisms in enzymes and transporters and conjugation level with glycine (Kerimi *et al.,* 2020).

Flavonoids

The flavonoids are divided into many subclasses such as flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols (Manach *et al.,* 2004). Previous studies showed that flavonoid glycosides are metabolised by many intestinal enzymes such as α-rhamnosidase, exo-β-glucosidase, endo-β-glucosidase and/or β-glucuronidase to form phenolic acids. For instance, rutin forms quercetin and quercetin is further biotransformed into 4-hydroxybenzoic acid 3,4-dihydroxybenzoic acid and 3,4-dihydroxyphenylacetic acids. It is also reported that these phenolic acids may be more bioactive than the parent flavonoid (Kim *et al.,* 1998).

Isoflavones are found in soya products mainly as glucosides. Studies suggested that transformation of isoflavones into its aglycone form is performed by intestinal β-glucosidases (Rowland et al., 2003). However, these biotranformations can be specific to some individuals. For instance, it was determined that transformation of dietary isoflavone daidzein into equol occurs only in one third of the people. A study investigating the capacity of fecal microbiota samples from 4 volunteers reported dihyrdodaidzein, *O*-desmethylangolensin and equol formation. The study showed that mixed bacterial cultures can transform daidzein into equol as community but fails to do so as pure cultures. This study emphasized the importance of cross-feeding effect of human gut microbiota on polyphenol metabolism. In addition, it was also suggested that addition of fructo-oligosaccharides can suppress equol production (Decroos *et al.,* 2005).

Isoxanthohumol (prenylflavonoid, phytoestrogen) can be degraded into 8-prenylnaringenin by instestinal microbiota. Due to inter-individual differences in 8-prenylnaringenin, some people were reported to be low 8-prenylnaringenin producers *(Bolca et al.,* 2007). A study tested whether addition of butyrate-producing *Eubacterium limosum* might enhance 8-prenylnaringenin in low producers. Fecal samples from high (Hop +) and low (Hop -) 8-prenylnaringenin producers were collected and examined in dynamic intestinal model plus Hop + and Hop- human microbiota associated rat models. Inclusion of *Eubacterium limosum* increased 8-prenylnaringenin production in high (Hop +) and low (Hop -) human microbiota fermentation and rat models (Possemiers *et al.,* 2008).

An *in vitro* study showed that human fecal microbiota degraded naringin into 3-(4-hydroxyphenyl)-propionic acid and 3-phenylpropionic acid and rutin into 3-hydroxyphenylacetic acid and 3-(3-hydroxyphenyl)-propionic acid. Degradation ratio was reported to be dependant on substrate concentration plus fecal microbiota composition (Rechner *et al.,* 2004). Human randomised trials also presented evidence on biotransformation of flavonoids into phenolic acids. For instance, a study reported presence of benzoic acid, hippuric acid, salicylic acid, phenylacetic acid, p-hydroxyphenylacetic acid and 3-(4-hydroxyphenyl)- 2-hydroxypropanoic acid in plasma within 3 h of blackcurrant juice consumption eventhough these phenolic acids were not detected in the juice (Jin *et al.*, 2011).

The parent compound of apigenin, apigenin-7-glucoside (A7G), shows antimutagenic, antiproliferative, and antiallergic effects. A study investigating the impact of human microbiota on bioavailability of the flavone apigenin-7-glucoside (A7G) compared germ-free and human microbiota-associated (HMA) rats. The study revealed that only 11 and 13% of the A7G dose were excreted within 48 h in both germ-free and HMA rats respectively. It was also shown that main A7G metabolites are apigenin and its conjugates which were mainly excreted with feces. On the other hand, 3-(4-hydroxyphenyl)propionic acid was the main metabolite in HMA rats and was predominantly recovered from urine. Results suggest that total excretion of A7G and its metabolites is low despite the microbial transformation takes place.

Table 2. Studies Reporting the Effect of Certain Microorganisms or Community based Gut Microbiota on Flavonoid Metabolism

Study Details	Flavonoids & (Source if reported)	Microorganisms	Reference
In vitro fermentation studies	Flavonoids glycosides: rutin, hesperidin, naringin, poncirin, baicalin, puerarin and daidzin	Community based human gut microbiota Role of α-rhamnosidase, exo-13-glucosidase, endo-13-glucosidase and/or β-glucuronidase from human gut is suggested.	Kim *et al.,* (1998)
	Isoflavone daidzein	Community based human gut microbiota, pure cultures failed	Decroos *et al.,* (2005)
	Naringin and rutin	Community based human gut microbiota	(Rechner *et al.,* (2004)
In vitro fermentation using dynamic intestinal model	Isoxanthohumol	*Eubacterium limosum*	Possemiers *et al.,* (2008)
Randomised, cross-over, double-blind, placebo-controlled trial	Anthocyanins (blackcurrant juice drink)	Not determined, colonic fermentation in gut suggested	Jin *et al.,* (2011)
Germ-free and human microbiota associated rat model	Apigenin-7-glucoside	Not determined, colonic fermentation in gut suggested	Hanske *et al.,* (2009)

However, it is certain that gut microbiota modifies the metabolite profile from the parent compound, A7G *(Hanske et al.,* 2009).

Green tea and oxidized black tea are good sources of catechins. Four main catechin forms are epigallocatechin gallate (EGCg), epigallocatechin (EGC), epicatechin gallate (ECg), and epicatechin (EC). Caco-2 models and rat studies on tea catechins show that absorption in small intestine is low (Chen *et al.,* 1997; Zhang *et al.,* 2004). Three main modifications were reported by gut microbiota on catechins. These include (i) galloyl ester hydrolysis, (ii) C-ring opening, and (iii) further modifications by lactonization, decarboxylation, dehydroxylation, and oxidation processes (Liu *et al.,* 2020).

Human intervention studies mostly report the fact that bioavailability of flavonoids is quite low. A study investigating the bioavailability of anthocyanins after acute cranberry juice consumption showed that it it was possible to detect in plasma and urine 7 of the 15 anthocyanins found in cranberry juice but recovery from cranberry juice was between 0.078 and 3.2% of the administered dose. Although it is reported that there is an inter-individual variation in recovery ratios, bioavailability of anthocyanins is still low (Milbury *et al.,* 2010). Some of the studies addressing the influence of gut microbiota on bioavailability of flavonoids are listed in the Table 19.2. Briefly, many studies report or suggest the effect of community based microbiota on flavonoids but only a few report the responsible microorganism at family or genus level.

Stilbenes

Stilbenes are found in red grapes, cranberries, strawberries, blueberries, peanuts and wine. Resveratrol is the most studied and known type. Although resveratrol has a lipophilic nature, mammalian model studies showed that its bioavailability is low (Chimento *et al.,* 2019). Briefly, resveratrol is absorbed in

the small intestine by passive diffusion or via membrane transporter and passes to the bloodstream in original form. Resveratrol can bind to albumin and lipoproteins once it get in the bloodstream. Binding to albumin or lipoproteins can also enhance its passage to the cells. Resveratrol is also subjected to phase II metabolism and resveratrol metabolites are formed. However, studies showed that resveratrol metabolites detected in the urine have low bioactivity. (Chimento *et al.,* 2019; Gambini *et al.,* 2015).

Studies were carried out to assess the role of human gut microbiota on bioavailability of resveratrol. For instance, Bode *et al.* (2013) performed in vitro fermentation experiments using fecal samples from 7 healthy volunteers plus a human intervention study (12 healthy volunteers included). In human intervention study, participants received oral dose of 0.5 mg *trans*-resveratrol/kg body weight. The study detected conversion of *trans*-resveratrol into dihydroresveratrol plus identified two new metabolites, 3,4'- dihydroxy-*trans*-stilbene and 3,4'-dihydroxybibenzyl (lunularin) both in vitro and in vivo. The study concluded that human gut microbiota metabolizes *trans*-resveratrol but there is a great inter-individual variability among volunteers (Bode *et al.,* 2013). *Trans*-resveratrol metabolism by human gut microbiota shows pronounced inter-individual differences which should be taken into account during investigation of health-related effects of this stilbene.

Gut bacteria also produces resveratrol from resveratrol precursors such as piceid so increases its bioavailability. *Bifidobacteria infantis* and *Lactobacillus acidophilus* were determined to be responsible for resveratrol production from piceid. Morover, resveratrol can be glycosylated in the gut and be tranformed into piceid again (Chaplin *et al.,* 2018).

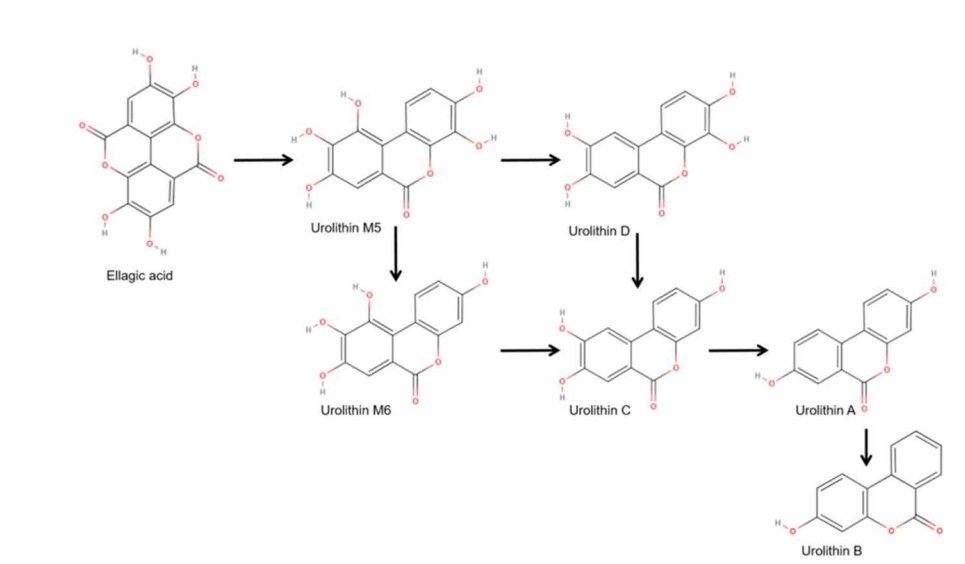
Ellagitannins

Ellagitannins are found in pomegranates, raspberries, strawberries, walnuts and almonds. Free ellagic acid can be released through acid hydrolysis of ellagitannins (Kawabata *et al.,* 2019) and ellagic acids are transformed into urolithins by gut microbiota (Al-Harbi *et al.,* 2021).

A human intervention study investigated the pharmacokinetics of pomegranate ellagitannins. The study included 18 healthy volunteers and the volunteers were given 180 mL of pomegranate juice concentrate. Blood samples were collected after 6 h. Urine samples were collected on day -1 (the day before study), day 0 and day +1 (the day after study). The study showed that ellagic acid was found in plasma of all subjects and the maximum concentration was 0.06 ± 0.01 μmol/L. The time of maximum concentration (0.98 ± 0.06 h) and half life (0.71 ± 0.08) were short, this indicates a quick formation and adsorption of ellagic acid. The study also showed that ellagic acid derivatives such as dimethylellagic acid glucuronide and hydroxy-6H-benzopyran-6-one derivatives (urolithins) are found were in plasma and urine in conjugated and free forms (Seeram *et al.,* 2006). Ellagitannins are reported to be stable in the acidic environment of stomach. In small intestine, these compounds are transformed into ellagic acid which is a poorly bioavailable compound. Gut microbiota can act on ellagic acid and produce urolithins which is way more bioavailable than ellagic acid. However, ratio of this biotransformation depends on gut microbiota composition and inter-individual differences takes place (Espín *et al.,* 2013; Tomás-Barberán *et al.,* 2014).

Producing urolithins from ellagic acid starts with hydrolysis of the one of the lactone moieties and formation of carboxylic acid which is later reduced to form a semi-hydroquinone. This intermediate product loses the p-hydroxy group releasing a water molecule and then decarboxylation takes place (Figure 19.1). Later subsequent dehydroxylation can occur and urolithins A, B, and C are formed (Seeram *et al.,* 2006; Tomás-Barberán *et al.,* 2014).

Figure 1. Biotransformation of Ellagic acid into Urolithins (adapted from Al-Harbi et al., 2021)



Proantocyanidins

Proanthocyanidins are formed by the condensation of single or multi-component of flavan-3-ols and are found in grapes, apples and chocolate (Kawabata *et al.,* 2019). In stomach partial degradation occurs due to acidic environment and oligomers are hydrolysed to epicatechin monomer and dimers. This was suggested to enhance the absorption in the small intestine (Spencer *et al.,* 2000). However, only a small number of proanthocyanidins are bioaccessible in the small intestine (Del Rio *et al.,* 2010). Meanwhile, microbiota can act on monomeric and oligomeric catechins in the gut. Microbial degradation forms 3-hydroxyphenylacetic acid, 3,4-dihydroxyphenylacetic acid, 3-(3-hydroxyphenyl)propionic acid, and 5-(30-hydroxyphenyl)-γ-valerolactone (Spencer *et al.,* 2000). A feeding study (20 healthy human volunteers) also showed that gut microbiota transforms green tea flavan-3-ols into polyhydroxyphenyl-g-valerolactones (Del Rio *et al.,* 2010).

Bioactive Peptides

Plant proteins can provide bioactive peptides which improve human health with their antioxidative, anti-inflammatory, antihypertensive, antihypercholesterolaemic, anticancer, antimicrobial effects. These bioactive compounds were also suggested to support delivery and bioavailability of many other bioactive compounds (Karaś *et al.,* 2017). Food industry can provide various types bioactive protein by-products such as milk proteins or rice soy proteins. Following the intake, peptides encounter with many digestive enzymes in the mouth, stomach and the small intestine. In small intestine, many additional enzymes from the enterocytes are secreted as well. These enzymes are expressed in the microvilli of the brush border membrane and within the glycocalyx including dipeptidyl-peptidases 3 and 4, glutamyl aminoopeptidase, membrane metallo-endopeptidase, transmembrane protease serine 4 and transmembrane protease serine 15 (Lundquist & Artursson, 2016).

To show any biological effects, bioactive peptides should be absorbed from the gastrointestinal tract. Different mechanisms are in place to achieve uptake of these peptides. These mechanims can be listed as: Paracellular transport through intercellular tight junctions, direct penetration of the epithelial cell-membranes, endocytosis/phagocytosis by cells, and active transport by specific carrier proteins. Studies on bioactive peptides reported inadequate evidence on ability of the dietary bioactive peptides to enter the hepatic portal system in physiologically relevant concentrations whereas there is enough evidence on bioavailability of the dipeptides and tripeptides (Chakrabarti *et al.,* 2018).

Peptides and aminoacids in the gut are also used to produce short chain fatty acids such as propionate and butyrate. It is estimated that low pH condition and presence of carbohydrates affect peptide and aminoacid fermentation in proximal colon but distal colon serves a better environment (Louis & Flint, 2017).

As bioactive peptides can be produced by microbial fermentation. Using Lactic acid bacteria is accepted as an effective way of producing bioactive peptides in fermentaton media or food fermentation processes. It is reported that around 13 g of protein and peptides/day was estimated to reach human colon (Louis & Flint, 2017). It is known that many peptides have the capacity to modulate human gut microbiota (Wu *et al.,* 2021). Human gut microbiota should have capacity to produce bioactive peptides from ingested proteins reached colon. However, there is limited information on this subject, especially on plant derived ones. A study investigated the milk peptides released in the gastrointestinal tract of mini-pigs. Six different dairy food matrices were given to the pigs, later duodenal effluents were obtained over a 5 h-period and analyzed by tandem mass-spectrometry. Production of bioactive peptides were also reported and that approves bioactive peptide production by gut microbiota as suggested in in vivo experiments (Barbé *et al.,* 2014).

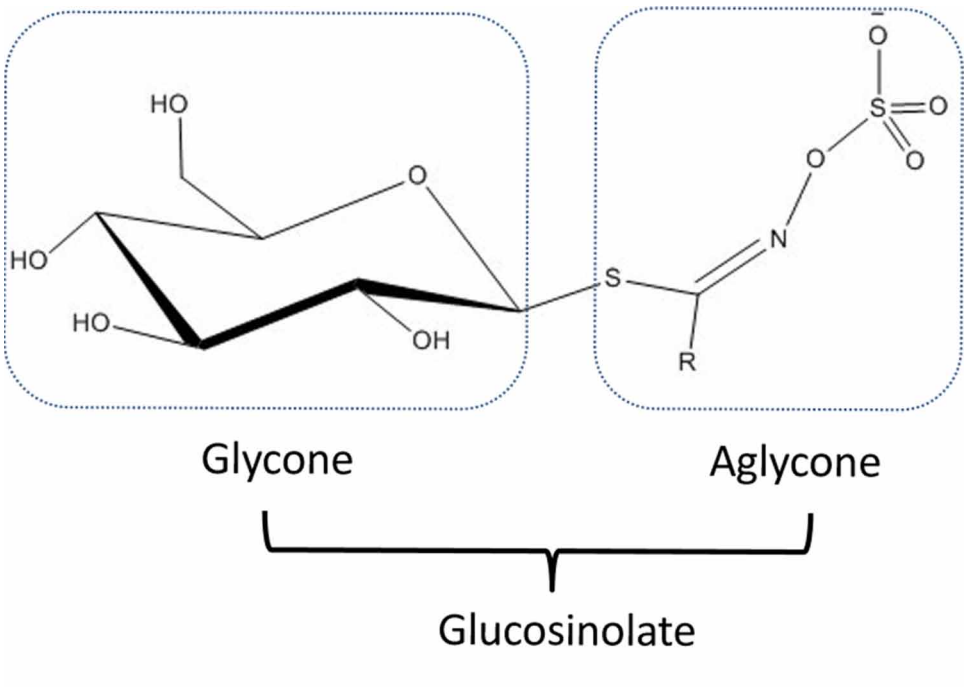
Glucosinolates

Glucosinolates are sulphur containing glycosides found in cruciferous vegetables mainly belong to the *Brassicaceae*, *Capparaceae* and *Caricaceae* genera. These include broccoli, radish, cabbage, Brussels sprouts, cauliflower and turnip of the different *Brassica* species. Glucosinolates have little biological activity but their degradation products serve as a defence against herbivores including insects, birds, aphids and mammals. Glucosinolates are also responsible for the characteristic flavour and odour of these vegetables. It was reported that they have antifungal and antibacterial properties (Fahey *et al.,* 2001). Glucosinolate research started with toxicological aspects of glucosinolates and methods for removing them from dietary sources and animal feed but nowadays, the studies are mainly focused on their potential health promoting effects (Narbad & Rossiter, 2018).

Glucosinolates (Figure 19.2) are degraded by plant myrosinases into bioactive isothiocyanates (ITCs) which have been recognised as potent anticancer compounds. Myrosinase (thioglucoside hydrolase EC 3.2.3.1) is the enzyme responsible for hydrolysis of glucosinolates. Normally, glucosinolate hydrolysis in plant is avoided by storing glucosinolate and the degradation enzyme in different plant compartments (Fahey *et al.,* 2001). Glucosinolate can generate various types of metabolites such as ITCs, nitriles, epithionitriles and thiocyanates. Table 19.3 shows some of the common glucosinolates found in cruciferous plants and their degradation products, ITCs.

The plant myrosinases are well studied and characterised. However, during cooking plant myrosinases are heat inactivated and this biotranformation relies on specific gut bacteria and their myrosinase-like enzymes that can metabolise glucosinolates into ITCs (Narbad & Rossiter, 2018). In addition, reductases are also involved in glucosinolate metabolism. They can reduce sulphoxide groups and produce their

Figure 2. General Structure of Glucosinolates. R; variable side chain (adapted from Halkier & Gershenzon, 2006).



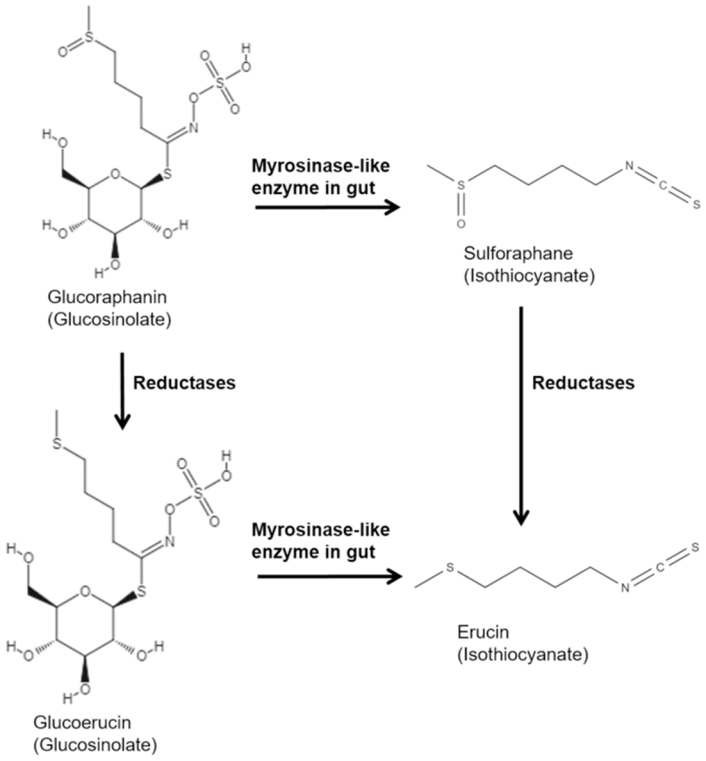
counterpart reduced glucosinolates (such as from glucoraphanin to glucoerucin) (Figure 19.3) (Cebeci, 2017).

Glucosinolates are well studied phytochemicals especially due to their bioactive degradation products. As different cooking methods destroy myrosinase activity from plant itself, ITC production by human gut microbiota becomes important to confer health promoting effects. However, there is limited information about formation of ITCs by human gut bacteria. There are studies including human intervention, rat models (Elfoul *et al.,* 2001) studies, gut community based in vitro fermentation models or in vitro fermentation assays using pure bacterial cultures (Luang-In *et al.,* 2014; Mullaney *et al.,* 2013b). These studies mainly show that there is an inter-individual difference in glucosinolate metabolism by human due to gut microbiota composition. It is known that many bacteria in human gut are involved in

Table 3. Some Important Glucosinolates and their Hydrolysis Products (adapted from (Luang-In et al., 2014)

Glucosinolate Precursor	Isothiocyanate Product	Nitrile Product
Sinigrin	Allylisothiocyanate	Allyl nitrile
Glucoerucin	Erucin	Erucin nitrile
Glucoiberin	Iberin	Iberin nitrile
From Gluconasturtiin	Phenethyl isothiocyanate	Phenethyl nitrile
Glucoraphanin	Sulforaphane	Sulforaphane nitrile

Figure 3. Proposed metabolism of glucosinolates into isothiocyanates by gut microbiota (adapted from (Cebeci, 2017)



glucosinolate degradation and glycoside hydrolases are involved in the metabolism but the responsible enzyme in the human gut is yet to be identified.

In vitro fermentation assays use human gut microbiota to assess their impact on glucosinolates in vitro. There are pioneer studies reporting glucosinolate degradading ability of pure bacterial strains in vitro. For instance, *Enterobacter cloacae* was identified as a sinigrin degrading bacterium in 1974 (Tani *et al.,* 1974b). Another study reported glucosinolate degrading ability of *Bacillus cereus* strains (Huber *et al.,* 1983) and Brabban & Edwards (1994) showed that *Bacillus*, *Streptomyces*, *Staphylococcus* isolates and an unknown fungus can degradee sinigrin. These strains were not isolated from the human gut but *Enterobacter*, *Bacillus* and *Staphylococcus* genera are also members of human gut microbiota. Later, in vitro fermentation assays were performed using pure bacterial cultures of human origin but some of these could not detect ITCs. Cheng *et al.* (2004) studied *Bifidobacterium pseudocatenulatum*, *Bifidobacterium adolescentis* and *Bifidobacterium longum* for their ability to utilise sinigrin and glucotropaeolin in vitro. The study concluded that these *Bifidobacterium* strains are able to utilize both sinigrin and glucotropaelin producing 3-butene-nitrile as main product. Phenylacetonitrile and AITC or benzyl isothicyanate (BITC) were hardly detectable.

Plant myrosinase (thioglucosidase) is a member of glycoside hydrolase family 1 (GH1). Studies also used bioinformatic tools to find myrosinase like enzymes of different bacterial species and determine myrosinase producers. Mullaney *et al.* (2013a) investigated three bacteria including *Lactobacillus plan-*

tarum KW30, *Lactococcus lactis* subsp. *lactis* KF147, and *Escherichia coli* Nissle 1917, and known myrosinase-producer *Enterobacter cloacae* to degrade the glucosinolates in broccoli extract. It was shown that Enterobacteriaceae degraded 65% of glucoiberin and 78% of glucoraphanin and transformed them mainly into their reduced counterparts glucoiberverin and glucoerucin, respectively. The study reported only a small amount of iberverin nitrile and erucin nitrile formation when Enterobacteriaceae was included. On the other hand, lactic acid bacteria consumed 30−33% of glucosinolates and produced nitriles such as iberverin nitrile, erucin nitrile, sulforaphane nitrile, and further unidentified metabolites (Mullaney *et al.,* 2013).

Luang-In et al investigated the metabolism of glucoerucin, glucoiberin and glucoraphanin by gut strains; *Lactobacillus agilis* R16, *Enterococcus casseliflavus* CP1, *Escherichia coli* VL8. *Lactobacillus agilis* R16 metabolised only 10% of glucosinolates and did not produce any detectable products. *E. casseliflavus* CP1 metabolised 40-50% of glucoiberin and glucoraphanin and resulted in formation of iberin and sulforaphane in low concentrations. *Escherichia coli* VL8 showed 80-90% degradation of glucoiberin and glucoraphanin. The metabolism by *E. coli* VL8 produced glucoiberverin from glucoiberin and glucoerucin from glucoraphanin. Other metabolites were erucin, erucin nitrile and iberverin, iberverin nitrile respectively which points a reductase activity. This reductase activity was proposed to performed by a reductase requires both Mg^{2+} and NAD(P)H as cofactors (Luang-In *et al.,* 2014). This study also supports the idea that reductases are also involved in glucosinolate metabolism by gut bacteria (Cebeci, 2017). A follow-up study using same *Lactobacillus agilis* R16, *Enterococcus casseliflavus* CP1 and *Escherichia coli* VL8 aimed to investigate the metabolic fates of sinigrin, glucotropaeolin, gluconasturtiin, and their corresponding desulfo-GSLs. Gluconasturtiin was completely degraded within 24 h to phenethyl isothiocyanate and phenethyl nitrile by all bacteria, excluding *L. agilis* R16 which produced only phenethyl nitrile. More than 80% of glucotropaeolin and sinigrin were degraded by all bacteria within 24 h to ITCs and nitriles. The total amount of the products only accounted for 3–53% of the initial glucosinolate amount. It was reported that Fe^{+2} promotes nitrile production, while Mg^{+2} does the same for ITC formation. In addition, the study showed that desulfoglucosinolates can only give rise to nitriles not ITCs or epithionitriles (Luang-In *et al.,* 2016). Crucifer specialists were reported to have sulfatase activity which enables them to produce desulfoglucosinolates from glucosinolates. This biotransformation prevents myrosinases to act on glucosinolates and form toxic hydrolysis products to specialists (Ratzka *et al.,* 2002).

Bacteroides thetaiotaomicron, a human digestive strain, was studied for its ability to degrade sinigrin in a gnotobiotic rat model. An oral dose of 50 μmol sinigrin was given to gnotobiotic rats harbouring *B. thetaiotaomicron*. Sinigrin was metabolised in the large bowel and, allyl isothiocyanate, hydrolysis product of sinigrin, was detected in digestive contents (Elfoul *et al.,* 2001). Another study investigated glucoraphanin degradation by 5 *Lactobacillus* species (*Lactobacillus gasseri*, *Lactobacillus acidophilus*, *Lactobacillus casei* and two *Lactobacillus plantarum* species). The degradation rate by the *Lactobacillus* species ranged from 36 to 49% after 24 h incubation and the main degradation product was nitrile, no sulforaphane was detected (Lai *et al.,* 2009).

Studies also investigate glucosinolate degradation by the microbial community instead of a certain type bacteria in rat models. For instance, Lai et al. (2009) showed that rat cecal microbiota was able to degrade 40% of the initial glucoraphanin in the medium after 24 h incubation. When rats were pretreated with glucoraphanin, degradation rate went up to 56%. The main hydrolysis product was reported to be nitrile. The study determined that isothiocyanate metabolites are formed and found in portal blood stream after introducing glucoraphanin directly to cecum. A following study to this examined ex vivo

degradation of glucoraphanin by rat cecal microbiota and reported evidence for glucoraphanin hydrolysis to sulforaphane and its absorption across the cecal walls of rats. Glucoraphanin (150 μmol/kg BW) was directly introduced to cecum and ITC were detected in the mesenteric plasma by 120 min and plasma levels keeping the stability for an hour (Lai *et al.,* 2010). A rat model study investigated glucosinolate hydrolysis in gnotobiotic rats. Rats harbouring a whole human faecal flora (Flora+) was compared with that in germ-free rats (Flora-). To test the effect of plant myrosinase, myrosinase was either active (Myro+) or inactive (Myro-) in the diets given to the rats. Urinary mercapturic acids which are end products of isothiocyanate metabolism were used o estimate isothiocyanate formation. The study concluded that highest excretion of urinary mercapturic acids was found when plant myrosinase was active (Myro+) in grem-free rats (Flora-). The excretion was lower in rats with whole human feacal microbiota (Flora+) and given active myrosinase (Myro+). Excretion of urinary mercapturic acids was low in rats harbouring a whole human faecal flora (Flora+) but Flora+ treatments also show promising capacity to break down glucosinolates as no intact glucosinolates were detected in the faeces of rats (Rouzaud *et al.,* 2003a). These results emphasize the importance of an active and efficient myrosinase to confer health benefits from glucosinolates.

Studies mostly report ITC formation and potential health benefits thanks to human gut microbiota (Krul *et al.,* 2002). However, some studies focus on the fact that other metabolites but yet ITCs can be produced such as allyamine or benzylamine (Combourieu *et al.,* 2001). Food matrix effect should also be taken into account when discussing bioavailability of bioactive compounds. For instance, plants include specifier proteins as they have myrosinases. In presence of specifier proteins, the hydrolysis of glucosinolates results in formation of nitriles, epithionitriles and organic thiocyanates instead of ITCs (Wittstock & Burow, 2007). Biological activity of these compounds are low compared to ITCs plus they can even show toxic effects such as thiocyanates (inhibit the uptake of iodide by the thyroid)(Eisenbrand & Gelbke, 2016; Wittstock & Burow, 2007).

Health claim on glucosinolates depends on ITC formation and its concentration but glucosinolate degradation not always end up by formation of ITCs. To determine the amounts of glucosinolate metabolite, a dynamic in vitro large-intestinal model was used. The study investigated sinigrin and its metabolites using human gut microbiota. Allyl isothiocyanate (from sinigrin) peak levels were observed between 9 and 12 h after the addition of sinigrin. The study reported that only 10% to 30% (mean 19%) of the sinigrin was converted into allyl isothiocyanate so rest of the sinigrin was supposed to be converted into unknown metabolites (Krul et al., 2002). Another in vitro fermentation assay using rat intestinal microbiota reported degradation of up to 64% of the initial sinigrin amount during 12h. The study showed that major products were allyl isothiocyanate (15% of initial sinigrin) and allyl cyanide (20% of initial sinigrin) after 12h. 1-cyano-2,3-epithiopropane was also detected in trace amounts in culture medium (Lu et al., 2011). This result raises the question about rest of the degraded sinigrin. Similar results were reported in another study testing the effect of human gut microbiota on glucoraphanin. The amounts of the metabolites detected by combined HPLC and LC–MS/MS methods did not account for the initial amount of the glucoraphanin in the media.

A human intervention study inclued 18 healthy volunteers consumed broccoli soups from fresh or frozen broccoli florets (lightly cooked before freezing). The study showed that glucoraphanin was converted into sulforaphane and sulforaphane was found in the plasma and urine as free form or sulforaphane thio-conjugates. In addition, the study reported reductase activity of gut microbiota forming glucoerucin from glucoraphanin. As Erucin N-acetyl-cysteine conjugate was also determined as a urinary metabolite, it was proposed that human gut microbiota can show myrosinase and reductase activity (Saha *et al.,* 2012).

Clarke et al. (2011) investigated the bioavailability and excretion of the mercapturic acid pathway metabolites of isothiocyanates after human consumption of fresh broccoli sprouts or broccoli supplement. The study was designed as a cross-over study in which 12 subjects consumed 40 grams of fresh broccoli sprouts followed by a 1 month washout period and then the same 12 subjects consumed 6 pills of a broccoli supplement. Control group was given alfalfa sprouts during the first phase and placebo pills during the second phase. The bioavailability of sulforaphane and erucin, main ITC products of brocoli, is siginificantly higher in fresh broccoli sprout consuming group. Interconversion of sulforaphane and erucin was also observed within each subject but this conversion was variable among the subjects. This study also confirms the importance of an active myrosinase to produce ITCs as stated in previous rat model study (Rouzaud *et al.,* 2003a).

Some of the studies reporting the effect of gut microbiota on glucosinolate metabolism are listed in Table 4. Briefly, many studies report the glucosinolate degradation by community based microbiota or pure bacterial cultures and glycoside hydrolases are suggested to be the responsible enzyme. Many attempts were also made to identify the gut microbial myrosinases (Liou *et al.,* 2020; Luang-In *et al.,* 2014). Some of these studies reported myrosinase activity by only intact cells but some showed myrosinase activity in cell-free extracts as well (Cebeci, 2017; Luang-In *et al.,* 2014).

MAIN FOCUS OF THE CHAPTER

This chapter mainly focus on biotransformation of phytochemicals by human gut microbiota. It discusses the studies (*in vitro* or *in vivo*) reporting or suggesting the gut microbial effect on different bioactive compounds.

SOLUTIONS AND RECOMMENDATIONS

The main concern regarding the effectiveness of phytochemicals in vivo raises from their low bioavailability profiles. Many studies report evidence for these bioactive compounds to show anticancer, antitumor, antiviral, antimicrobial, antiinflammatory and cardioprotective effects. Unfortunately, the concentration used in in vitro experiments are rarely applicable in vivo so this raises question about the real effectiveness of these molecules. To overcome this, further human feeding trials using in vivo applicable doses are needed.

FUTURE RESEARCH DIRECTIONS

As discussed in the chapter, human gut microbiota influences bioavailability of phytochemicals. However, our knowledge on this subject is limited for some phytochemicals. For instance, phenolic compounds are generally known to be metabolized by gut community but studies mostly lack identification of specific responsible microoorganisms. Identification of specific microorganism or responsible enzymes can help enhancing bioavailability of phytochemicals as some of them show very low bioavailability. In addition, studies mostly focus on bacteria but the role of other micoorganisms such as fungi should also be adressed. Another issue, human feeding studies mostly use bioactives in pure forms however presence of

other compounds change how microorganisms act on phytochemicals and which metabolites are formed. Briefly, more studies are needed to adress food matrix effect on bioavailability.

Table 4. Studies reporting the effect of certain microorganisms or community based gut microbiota on glucosinolate metabolism

Study Details	Glucosinolates & (Source if given)	Microorganisms	Reference
In vitro fermentation studies	Sinigrin	*Enterobacter cloacae*	(Tani *et al.,* 1974a)
	Glucosinolates, (defatted rape seed meal)	*Bacillus cereus* strains Trichosporon cutaneum (yeast)	(Huber *et al.,* 1983)
	Sinigrin	*Bacillus*, *Streptomyces* *Staphylococcus* and unknown fungus	(Brabban & Edwards, 1994)
	Sinigrin Glucotropaeolin	*Bifidobacterium pseudocatenulatum,* *Bifidobacterium adolescentis,* *Bifidobacterium longum*	(Cheng *et al.,* 2004)
	Glucoraphanin (broccoli extract)	*Lactobacillus plantarum* KW30 *Lactoccoccus lactis* subsp. *lactis* KF147 *Escherichia coli* Nissle 1917 *Enterobacter cloacae*	(Mullaney, Kelly, *et al.,* 2013)
	Glucoerucin Glucoiberin Glucoraphanin	*Lactobacillus agilis* R16 *Enterococcus casseliflavus* CP1 *Escherichia coli* VL8	(Luang-In *et al.,* 2014)
	Sinigrin, Glucotropaeolin, Gluconasturtiin Desulfo-glucosinolates	*Lactobacillus agilis* R16 *Enterococcus casseliflavus* CP1 *Escherichia coli* VL8	(Luang-In *et al.,* 2016)
Gnotobiotic rat model	Sinigrin	*Bacteriodes thetaiomicron*	(Combourieu *et al.,* 2001)
	Glucoraphanin	Not determined, colonic fermentation in gut suggested	(Rouzaud *et al.,* 2003b)
Cecal microbiota from male F344 rats	Glucoraphanin	*Lactobacillus gasseri* *Lactobacillus acidophilus* *Lactobacillus casei* *Lactobacillus plantarum strains*	(Lai *et al.,* 2009)
Rat intestinal microbiota	Desulfosinigrin	Community based human gut microbiota	(Lu *et al.,* 2011)
In vitro fermentation using dynamic intestinal model	Sinigrin	Community based human gut microbiota	(Krul *et al.,* 2002)
Human intervention study	Glucoraphanin (broccoli sprouts or broccoli suplement	Community based human gut microbiota (inter-individual variation due to gut microbiota composition)	(Clarke *et al.,* 2011)
	Glucoraphanin (broccoli soup)	Community based human gut microbiota	(Saha *et al.,* 2012)

CONCLUSION

The studies reveal that many microorganisms are involved in transformation of pytochemicals into their metabolites. Sometimes, these metabolites are more bioactive than parent compounds and in some cases they can be toxic to host as well. For certain phytochemicals, it was known that which enzymes in the gut are involved in biotansformation. For instance, α-rhamnosidase, exo-β-glucosidase, endo-β-glucosidase and/or β-glucuronidase are suggested to be involved in flavonoid degradation and gut bacterial myrosinases (possibly glycoside hydrolases), reductases (such as methionine reductases), sulfatases in glucosinolate degradation. However, further studies are needed. Various studies emphasize that there is inter-individual diffences among people in phytochemical metabolism. The knowledge we have about pytochemical bioavailability shoud enable us to develop better strategies. By doing so, it would be possible to enhance the biavailability of these compounds and make the most of them.

In conclusion, it was aimed to provide a better understanding of microorganisms and their enzymes involved in pytochemical metabolism to maximise the health benefits. Such understanding can lead us identification of probiotic strains to enhance the bioavailability of phytochemicals. This would improve the efficiency of these bioactive compounds for people who are unable to utilise phyochemicals and benefit efficiently.

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Chapter 7
Medicinal Plants for Gastrointestinal Diseases

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ABSTRACT

Gastrointestinal (GI) diseases are those that affect the digestive tract. This may include sections from the esophagus to the rectum and the liver, gallbladder, and pancreas digestive organs. Gastrointestinal diseases may be acute, chronic, or recurrent. Natural products show the potential ability to treat the causes and decrease the GI tract production systems. This chapter is to present some of the medicinal plants that are used to treat and minimize signals of GI disease pathogenesis.

INTRODUCTION

Gastrointestinal diseases are diseases affecting food intake, drinking water, and general health. Gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), irritable bowel syndrome (IBS), functional gastrointestinal disorder (FGD), inflammatory bowel disease (IBD), ulcerative colitis (UC), are several popular forms of digestive diseases. Gastroesophageal reflux disease (GERD) is a widespread condition with a rate as high as 10%-20% in the western countries, less than 5% in Asia (Badillo & Francis, 2014). The disease has various symptoms such as clinically troublesome heartburn, regurgitation, chest pain. There are also other atypical symptoms that may be associated with GERD such as: nausea, epigastric

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pain, dyspepsia, and belching. The protein targets of treatment for GERD are histamine H2 receptor (H2R) or proton-pump (Katz *et al*., 2013).

The statistical incidence of peptic ulcer disease (PUD) from hospitalization data is approximately 0.03–0.17% and 0.10–0.19% physicians diagnosed PUD (Sung *et al*., 2009). The main symptom of peptic ulcer disease is stomach pain. In addition, some more severe cases can lead to complications such as gastroduodenal hemorrhage and perforation of the stomach, which is the main cause of high mortality in patients with peptic ulcer disease. The most common cause of PUD is related to the side effects of non-steroidal anti-inflammatory drugs (NSAIDs) and the presence of Helicobacter pylori bacteria. The goal of most medicines is therefore close to GERD in addition to treating the etiology like antibiotics (Fashner & Gitu, 2015).

Irritable bowel syndrome (IBS) is a chronic digestive disorder that affects approximately 3–20% of the population of the United States. In Vietnam, the incidence of this disease is about 15-20%, it is common in people between the ages of 40-60. Poor knowledge of the pathophysiology and causes of IBS is provided. IBS has no usual signs and it is only discovered when the patient experiences abdominal pain along with bowel abnormalities such as diarrhea or constipation and general weakness if no abnormalities are present. morphological, histological or inflammatory when there is no the abnormal morphological, histological or inflammatory markers (Grundmann & Yoon, 2010). Several reports have lately demonstrated that the etiology of IBS is attributable in part to changes in the function of the nerves that feed the gastrointestinal tract, activation of the immune system and psychological causes. Enteric P2X receptors may affect gastrointestinal activities like propulsion and secretion, and the drugs acting at these receptors could be useful for treatment IBS (Galligan, 2004). Dyspepsia is known to signify chronic or episodic symptoms of abdominal pain or nausea and it involves the upper gastrointestinal tract (Heading, 1991). Functional gastrointestinal disorders (FGD) are common, accounting for up to 50% of gastroenterology referrals (Jackson *et al*., 2000). FGD is a condition whose Symptoms should be clear to allow a diagnosis of FGD for at least 12 weeks of the previous year. Of course, it has exceptions. An example of an exception is persistent abdominal pain that requires symptoms for six months, while other minors while anorectal pathologies only require symptoms for a few weeks. The cause is not clear so most medicines treat symptoms primarily (Drossman, 1999).

Inflammatory bowel disease (IBD) is a disease in which the digestive tract is damaged, chronic inflammation. IBD is ranked as the 5 most common gastrointestinal disorders in the United States, with total healthcare expenses costing more than $1.7 billion, and is a chronic illness (Malaty *et al*., 2010). Genome-wide association studies have identified multiple inflammatory bowel disease (IBD) susceptibility loci, including proteins involved in cytokine signaling and genes encoding cytokines. In particular, loss-of-function mutations in genes encoding IL-10 and the IL-10 receptor have been shown to be associated with early onset of IBD. And TNF-specific antibodies can induce mucosal healing in IBD and inhibit chronic intestinal inflammation (Neurath, 2014). Ulcerative colitis (UC) is a disease that affects 1-2 million people in the United States, and many more globally. Some symptoms include: abdominal pain, diarrhea, weight loss, bloody stools, fatigue, and fever. The precise cause of ulcerative colitis is unknown, the hereditary and environmental variations are risk factors. Several research have shown that the immune system is associated with UC (Colitis–Pathophysiology, 2003). Platelets may be triggered dramatically in UC. This can lead to vascular endothelial damage and upset the balance between TXB2 and 6-keto-PGF1a in blood (Dong *et al*., 2004).

This has been demonstrated that medicinal plants reduce the effects of different diseases like GI diseases. The effect of complete medicinal plant extract on GI disorders has been shown in several reports.

Specific molecules such as flavonoids, anthranoids, triterpenes, and alkaloids have shown numerous beneficial pharmacology behaviors in GI diseases. We will summarize some medicinal plants used for treatment of GI diseases below.

Medicinal Plants Used for Treatments of Gastrointestinal Diseases

Carica Papaya

Carica papaya L. (Caricaceae) is normally known for its food and dietary benefits. Papaya organic product is a rich wellspring of supplements like provitamin A, vitamin B, vitamin C, carotenoids, lycopene, L-ascorbic acid, dietary fiber and dietary minerals. It is known similarly as with diuretic ready and treatment heartburn. The *Papaya* fruit is purgative which guarantees of customary defecation. The smooth juice which is tapped from the green, mature natural product while still in the tree contains a compound known as "papain" which is utilized in various solutions for heartburn (Yogiraj *et al*., 2014). In addition, *Carica papaya* has also been shown to have a healing effect on the stomach. In an experiment on rats with stomach ulcers caused by aspirin, they were given 400mg/kg of *Carica papaya* fruit extract orally for 7 days and the ulcer index was significantly reduced (Ologundudu *et al*., 2008).

Zingiber Officinale

Zingiber officinale is a medicinal herb that has an important role and is widely used in medicine in Vietnam, China, Ayurveda, Siddha, etc. Ginger contains various nutrients such as fats, proteins, fibers, carbohydrates, proteases, lipids, essential vitamins, and minerals for the body. It also contains vitamins such as thiamine, riboflavin, niacin, and vitamin C. These substances can be isolated from *Zingiber officinale* as gingerols, adenine, acetoxy-6-dihydroparadol, shogaol, paradol, and 2,3-dihydroxy hexacosanoic acid, propyl ester, maleimide-5-oxime, etc (Kumar *et al*., 2011). The extract of Ginger has anti-inflammatory and antioxidant properties, that can reduce the severity of ulcerative colitis (El-Abhar *et al*., 2008). Studies in rats also shown an inhibitory effect on gynecomastia of this herbals. In addition, ginger is effective in curing spasms caused by isolated acetylcholine or by electrical stimulation (EFS). Ginger inhibits both of these contractions more strongly than inhibits EFS-induced contractions (Borrelli *et al*., 2004). Moreover, the methanol extracts of *Zingiber officinale* (ginger rhizome/root) and Rosmarinus officinalis (rosemary leaf) were assessed for the susceptibility of fifteen H. pylori strains had with MIC of 25 μg/mL, which is useful in peptic ulcer disease (Mahady *et al*., 2005).

Cynara Scolymus

Cynara scolymus is a traditionally consumed vegetable in many countries. This herbal contains some chemical composition like polyphenol, axit caffeic, axit chlorogenic, flavonoid, quercetin, gallic acid and ascorbic acid và cynarin and antioxidant properties (Lutz *et al*., 2011). *Cynara scolymus* has several good effects in the gastrointestinal tract. Artichoke extracts which were well tolerated, had a strong prebiotic influence on the composition of human faecal microbiota. A study was conducted to evaluate the effect of *Cynara scolymus* leaf extract on healthy volunteers with dyspepsia, the result showed a 26.4% reduction in the incidence of IBS after treatment.

Aloe vera

Aloe vera is a succulent plant belonging to the lily family, it has good drought tolerance. Since ancient times, *Aloe vera* has been known and used by people as a medicine to help treat constipation, wounds, coughs, diabetes, anti-cancer and many other diseases. *Aloe vera* gel includes over seventy bio active compounds such as anthraquinones, carbohydrates, chromones, lupeol, salicylic acid, urea nitrogen, cinnamic acid, phenols and sulfur, proteins, vitamin A, B12,C, E, choline and folic acid, auxins and gibberellins (Verma, 2011). And it is claimed to have healing, anti-inflammatory, anti-oxidant, anti-ageing, anti-cancer and immune boosting properties (Hutchings *et al*., 2011). *Aloe vera* gel can reduce symptoms in patients with mild to moderately active UC. It has been shown to be safer and more effective than a placebo. (Langmead *et al*., 2004). A study on the treatment of symptoms of gastroesophageal reflux disease (GERD) with *Aloe vera* found that it was more effective when compared with the benefits of omeprazole and ranitidine (Panahi *et al*., 2015). Moreover, this herbal also has the therapeutic potential of inflammatory bowel disease (IBD) and is recommended for the treatment of symptoms of irritable bowel syndrome (IBS) symptoms (Davis *et al*., 2006).

Cleistocalyx Operculatus (Roxb.)

The flower buds of *Cleistocalyx operculatus* are found in many herbal products and herbal teas. From the shoots of *C. operculatus*, 55 essential oil compounds were isolated. The oil was able to significantly inhibit the growth of food-borne bacteria (FB), food spoilage (FS), methicillin-resistant *Staphylococcus aureus* (MRSA), skin pathogens (SP), multi antibiotic-resistant bacteria (MARB), and vancomycin-resistant *Enterococci* (VRE). The ethanol extract demonstrated superior antibacterial activity against all gram-positive bacteria and a gram-negative food spoilage bacterium known as *P. aeruginosa* (Dung *et al*., 2008). The leaves of *Cleistocalyx operculatus* contain methanolic which have anticaries activity against *S. mutans* in acid production and biofilm formation (Nguyen *et al*., 2017). Extracts of *Cleistocalyx operculatus* buds have anti-inflammatory activity, reducing inflammatory responses by blocking the expression of inflammatory cytokines. In a study on RAW 264.7, a mouse macrophage-like cell line, was shown to significantly inhibit the lipopolysaccharide (LPS) secretion of C. operculatus shoots. This leads to a decrease in inflammatory factors such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which in turn suppresses the mRNA production of TNF-α and IL-1β (Dung *et al*., 2009). The study in an experimental LPS-induced sepsis rats model and in macrophages showed that both ethanol extract of flower buds (ECO) and its major constituent increased the nuclear translocation of the nuclear factor erythroid 2-related factor 2 (Nrf2), as well as the expression of Nrf2 target genes, including heme oxygenase-1 (HO-1), in macrophages (Tran *et al*., 2019).

Rheum palmatum L (Rhubarb)

Rheum palmatum is a perennial plant native to Asia. It includes the genus Rheum, which is in the *Polygonaceae* family. *Rheum palmatum* have an extended background of mainstream Vietnamese and Chinese medicine as medicinal plants. The roots and stems contain a lot of anthraquinones, like rhein and emodin (1,3,8-trihydroxy-6-methyl-9,10-anthraquinone). They have a laxative effect, which explains the frequent misuse of *Rhubarb* as a slimming agent (Ashnagar *et al*., 2007). *Rheum palmatum* has many

pharmacological effects, including anti-inflammatory, anticancer, nephroprotective, hepatoprotective, antioxidant, and antimicrobial activities (Zhou *et al*., 2015).

Cassia angustifolia Vahl.

Cassia angustifolia Vahl. is a precious medicinal plant that has been used by humans to treat díeases for several thousand years in Vietnam, China, Saudi Arabia, Egypt, Yemen (Deshpande & Bhalsing, 2013). The pods and leaves have two anthraquinones: Sennoside 'A' and sennoside 'B', well known in pharmaceutical industry as a medicinal laxative. The plant also contains aloe-emodin, emodin, chrysophenol and rhein. There is also a naphthalene glycoside known as tinnevellin glycoside (0.3%) in this plant. Various medicines from *Cassia angustifolia* such as Nilaavarrai Choornam of Siddha medicine are indicated for constipation, bloating, and flatulence; the powder of the dried leaf is taken as a purgative for treatment constipation, abdominal distention (Ramchander & Middha, 2017). Senna is often used as a febrifuge in anemia,, splenic enlargements, cholera, typhoid, jaundice, biliousness, rheumatism, gout, bronchitis, and tumors (Mehrafarin *et al*., 2012).

Cassia nigricans

Cassia nigricans is an annual herb, or under shrub. It is widely grown in tropical Africa, such as India, Arabia and Nigeria (Deshpande & Bhalsing, 2013). The leaves of *Cassia nigricans* has several bio active substances such as emodic acid, emodin, a flavonoid – luteolin, citreorosein, hydroxyestranic acid and ethyl ester. *Cassia nigricans* has many beneficial effects in the treatment of gastrointestinal disorders like ulcers and diarrhea. The methanol extracts from the leaves have been shown to possess important antiulcerogenic effects, evidently regulated by histaminergic receptor inhibition. It also had a short-acting effect, reducing intestinal contractility and increasing castor oil-induced diarrhea in mice (Ayo, 2010).

Cassia fistula

Cassia fistula L., a semi-wild Indian Labernum, is widely grown in Mauritius and some areas in Southeast Asia, Sri Lanka and southern Pakistan. In Vietnam, it has been used as medicine since ancient times. The xanthone gllycosides and flavonol reported from the plant's bank, which have beneficial effects for treating some diseases. A stem bark powder has some compounds like: β-sitosterol, hexacosanol, lupeol, tannins. The pulp contains carbohydrate 26.30%, protein 19.94%, glutamid, acid leucine and arginine. The pods contain astringent matter, fistulic acid, matter, gluten, sugar; Seed contains malvalic acids, vernolic oil, and sterculic. *Cassia fistula* has been shown to have antipyretic, astringent effects and is also used as a tonic (Sundaramoorthy *et al*., 2016). Flowers have the effect of astringent, wound healing, febrifugal, the decoction of flowers is used to treat symptoms of abdominal pain, indigestion (Jothy *et al*., 2011). It is shown that the in-vitro effect of *Cassia fistula* infusion on isolated guinea-pig ileum and *Cassia fistula* is suggested to be safely used as a laxative or as its substitute (Danish *et al*., 2011).

Ricinus communis

Ricinus communis, which is related to the Euphorbiaceae family, is also called Castor oil plant in English. The plant is known first from India and is grown in some countries in gardens and fields and

also grows in wild places. This herbal contains various compounds include leaves contain disaccharide glycoside rutin, gentistic acid, quercetin, and gallic acid; seeds contain proteins Ricin A, B and C and one ricinus agglutinin; fruit contain alkaloid, ricinine (Rana *et al*., 2012). At a dose of 500 mg/kg, *R. communis* seed castor oil also had anticoagulant properties, and a dose of 1000 mg/kg was more effective in mucosal protection, against the ulceration caused by pylorus, ethanol, and aspirin in mouse (Jena & Gupta, 2012). Furthermore *R. communis* oil can be used in cases of inflammation of the intestine or dysentery (Singh *et al*., 2010).

Solanum Nigrum

Solanum nigrum L. is widespread in south Asia, which belongs to the Solanaceae family, and has known as traditional folk medicine. Stems are often angular, sparsely-pubescent. The fruits contain several compounds such as polyphenols and anthocyanidin. *Solanum nigrum* leaves contain apigenin, gentisic acid, kaempferol, luteolin, and m-coumaric acid with the highest concentration (Huang *et al*., 2010). *Solanum nigrum* is used to manage gastric ulcers. *Solanum nigrum* fruits extract decreases gastric secretory volume, pepsin secretion in ulcerated rats. The results obtained showed a significant reduction in ulceration after 7 days of treatment with *Solanum nigrum* fruits extract (200 and 400 mg/kg body weight). It is also shown that *S. nigrum* fruits extract inhibits H+K+ATPase activity and decreases the gastrin secretion in ethanol-induced ulcer models (Jainu *et al*., 2006). In addition, some studies have indicated that *S. nigrum* berries can use a free radical scavenging action to exert their gastroprotective effect. *S. nigrum* berries can have significant therapeutic potential for treating gastric diseases (Chauhan *et al*., 2012).

Psidium Guajava

Psidium guajava is not only a food crop but also a crucial medicinal plant in tropical and subtropical countries. It contains flavonoid, phenolic, terpenoid, carotenoid and triterpene; seeds even have rich proteins, starch, oils and flavonoid compounds. The main constituents of guava leaves are catechin, gallic acid, epicathechin, isoflavonoids, naringenin, kaempferol, phenolic compounds, and rutin. The pulp is rich in antioxidants, carotenoids (lycopene, β-carotene and β-cryptoxanthin). *Psidium guajava* is principally known for its antimicrobial and antispasmodic properties within the treatment of dysentery and diarrhoea. Quercetin present within the leaf extract has been proposed as a possible means of managing acute diarrheal disease because it inhibited gastrointestinal release of acetylcholine (Gutiérrez *et al*., 2008). The crude extract of *Psidium guajava* (100-1000 mg/kg) in castor oil-induced diarrheal model has benefits on gut motility as a loperamid, utilized in treatment of hyperactive gut disorders (Gilani *et al*., 2011). In fact, several pharmacological trials have shown this plant's capacity to demonstrate antioxidant, antispasmodic, anti-allergy, antimicrobial, antigenotoxic, antiplasmodial, anti-cough, antidiabetic, cardioactive, cytotoxic, hepatoprotection, anti-inflammatory and antinociceptive activities.

Cassia Tora

Cassia tora is a precious medicinal plant that has been widely used by humans in traditional medicine. It is found commonly in Vietnam, India, China and other tropical countries. This plant has isolated some active compounds such as glycosides, anthraquinone, flavonoids, phenolic compounds, naphthopyrone glycosides, etc. (Pawar & D'mello, 2011). In traditional medicine, the leaves are anti-patriotic, alterative,

aperients, and given to children having intestinal disorders. The leaves, roots, and even the whole plant are used in the treatment of impetigo, ulcers, helminthiasis purgative. Doses of 5 to 15 ml of decoction of leaves have a mild laxative (Bhandirge *et al*., 2016). Hydroalcoholic extract of *Cassia tora*, which was used orally, showed reduced formation of ulcers, free acidity and total acidity in ethanol induced gastric ulcer model in Wistar albino rats (Gulia & Choudhary, 2012).

Garcinia cambogia

The fruit rind of Garcinia cambogia contains components are mainly benzophenones (e.g. garcinol) and xanthones (e.g. carbogiol) together with organic acids and amino acids (e.g. gamma aminobutyric acid). The main organic acid component of the fruit skin is hydroxycitric acid, which has anti-obesity effects, decreased *de novo* lipogenesis and increased fat oxidation (Semwal *et al*., 2015). The administration of garcinia to colitic rats improved macroscopic damage, reduced colonic levels of PGE2 and IL-1β and decreased in COX-2, MPO activity and iNOS expression (dos Reis *et al*., 2009). In addition, *Garcinia cambogia* has the capacity to reduce the acidity and to increase the mucosal defence in the damaged gastric mucosa induced by indomethacin (Mahendran *et al*., 2002).

Ginkgo biloba

Ginkgo biloba L., which is also known by several other names such as *Salisburia adiantifolia*, *Salisburia macrophylla*, and *Pterophylla salisburgensis*, belongs to the Ginkgoaceae plant family. Low molecular weight flavonoids are common substances in this plant. The Ginkgo leaf extract contains biflavones (amentoflavone, bilobetol, 5-methoxybilobetol, ginkgetin, isoginkgetin and sciadopitysin), flavones, flavonols, and tannins, (Mahadevan & Park, 2008). *G. biloba* extract has antioxidant effects that can be used to treat colitis in mice (Kotakadi *et al*., 2008). Zhou *et al*., had indicated that *G. biloba* extract could reduce histological and macroscopic damage, enhances superoxide dismutase enzyme activity in the colon tissues of experimental colitis (Zhou *et al*., 2006). Methanol extracts of *G. biloba* (leaves) also have the ability to decimate the gram-negative bacterium *Helicobacter pylori* which related to redevelopment of gastritis and peptic ulcer disease with MIC > 100 μg/mL (Mahady *et al*., 2005). Moreover, *G. biloba* also inhibited the ethanol-induced gastric injuries in mice by inhibition of lipid peroxidation and preservation of gastric mucus (Chen *et al*., 2005).

Angelica sinensis

Angelica sinensis is one of the most normally used traditional Chinese medicines in China. The plant has some compounds are active components of *Angelica sinensis* such as aromatic compounds, ferulic acid, terpenes, Z-ligustilide, Z-butylidenephthalide, phthalides, polysaccharides (Lin *et al*., 1998). *Angelica sinensis* can relieve endothelial vascular cell, inhibit platelet activation, and improve microcirculation in patients with ulcerative colitis (Dong *et al*., 2004). *Angelica sinensis* polysaccharide has a protective effect on immunological colon injury in rats model, which may be due to the mechanism of antioxidation, immunomodulation and promotion of wound repair (Liu *et al*., 2003). *Angelica sinensis* heals gastric mucosa directly through an EGF-mediated pathway (Ye *et al*., 2001).

Camellia sinensis

Camellia sinensis (tea) has originated in China and was cultivated in various Asia countries like Vietnam, India, etc. There are two major types of tea, green tea and black tea. They both contain caffeine (1–5%) with small amounts of other xanthine alkaloids. Tea also contains large amounts of tannins or phenolic substances (5–27%) including gallic acid units and catechin (flavanol), which are lower in black tea than in green tea (Khan & Abourashed, 2011). In general, fresh green tea leaves contain 36% polyphenols, among which catechins prevail. The pharmacological properties of tea are mainly due to its catechins and alkaloids (caffeine), which are divided into four main compounds, epigallocatechin (EGC), epicatechin (EC), epigallocatechin gallate (EGCG), epicatechin gallate (ECG), and four secondary compounds are catechin (C), gallocatechin (GC), gallocatechin gallate (GCG), and catechin gallate (CG). EGCG is the main catechin found in green tea leaves (48–55%) (Perva-Uzunalić *et al*., 2006). Moreover, the hot water extract of black tea possesses anti-ulcer activity (Maity *et al*., 1995).

Saussurea Lappa

Saussurea lappa is a common plant and has several medicinal uses in India, Korea, China and other Asian countries. Various potential compounds had been isolated such as β- cyclocostunolide, costunolide, dihydro costunolide, dehydro costuslactone, and sesquiterpene, etc. (Liu *et al*., 2012; Robinson *et al*., 2008). The best known effect of this herbal is anti-inflammatory effect through cynaropicrin, a sesquiterpene lactone from *Saussurea lappa* (Cho *et al*., 2000). Ko *et al.,* (2005) showed that extracts of *Saussurea lappa* root can be a good choice against gastric cancer. Moreover, *Saussurea lappa* has a gastroprotective effect through some substances like costunolide, dehydrocostus lactone and saussureamines A, B and C on acidified ethanol-induced gastric mucosal lesions in rats (Matsuda *et al*., 2000).

Azadirachta Indica

For over 2000 years, *Azadirachta indica* has been known as one of the most traditional medicinal plants in Asian countries, especially India and China, for its wide range of biological effects. *A. indica* leaf extract induces antiulcer effects in rats orally exposed to cold stress or ethanol by preventing mucus accumulation and mast cell degranulation. The Aqueous extracts contain Azadirachtin A, B, D, H, I, Azadirone, Azadiradione, Desacetylnimbin, Nimbin, Nimbolin, Nimbinene, Nimbolide, Salanin (Sadeghian & Mortazaienezhad, 2007). Biswas *et al*., indicated that the *A. indica* leaf extract was noted to have potent antacid secretion and antiulcer activity, and the bioactive compounds, whose effects were attributed to glycosides (Biswas *et al*., 2002).

Cissus quadrangularis

Cissus quadrangularis L. belongs to the family Vitaceae and has been used by common man in India, China for promotion of fracture healing (Mishra *et al*., 2010). The insulation compounds from this plant's stems are stilbenes resveratrol, piceatannol and pallidol, flavonols, quercetin, kaempferol etc. (Adesanya *et al*., 1999). *Cissus quadrangularis* has various potential medical effects, including gastroprotective activity when conjugation with NSAID therapy (Mishra *et al*., 2010). *C. quadrangularis* extract promotes ulcer healing by decreasing gastric secretion and increasing gastric mucin content and

concentration, increasing glycoprotein level (Jainu *et al*., 2006). In the mouse model, *C. quadrangularis* extract treatment helps restore gastric mucosal epithelium thereby reducing the size of ulcers. In addition, *C. quadrangularis* extract reduces neutrophil infiltration and has antioxidant and anti-infective activity, which plays an important role in gastric defense (Jainu *et al*., 2006).

Pogostemon cablin

Pogostemon cablin which belongs to the family Laminaceae, is an erect, bushy herbaceous plant growing to 75 cm tall. Its flowers are small, pinkish-white in color. The main chemicals of this plant are alkaloids, alcohols, α-patchoulene, α-bulnesene, β-patchoulene terpenoids, eugenol, phytosterols, flavonoids, organic acids, ligninsglycosides, norpatchoulenol, seychellene, pogostone and pogostol. In traditional medicine, *Pogostemon cablin* is used to fight fever, nausea, vomiting, diarrhea, abdominal pain, colds, and headaches. In recent time, studies showed various biological effects like, analgesic, aphrodisiac, antiemetic, antioxidant, antidepressant, anti-inflammatory, antiplatelet, antithrombotic, antimutagenic, cytotoxic and activities fibrinolytic (Swamy & Sinniah, 2015). Yang *et al* also indicated that the *n*-hexane extract of *Pogostemon cablin* has the ability to exhibit anti-emetic effects (Yang *et al*., 1999). In addition, *Pogostemon cablin* water extract suppressed colon inflammation (Park *et al*., 2014).

Grapefruit seeds

Grapefruit seeds contain various glycosides, flavonoid, naringenin, quercetin, hesperidin, kaempferol and apigenin. Grapefruit seed extracts contain flavonoids, which has been shown to have antibacterial, antifungal and antiviral activities (Drozdowicz *et al*., 2011). Grapefruit seeds extract has a strong gastroprotective effect against gastric injury through a rise in the asembly of endogenous prostaglandins, unquestionably mediated hyperemia via nitric oxide NO and inhibition of lipid peroxidation, and co-administration of exogenous calcitonin-related peptides, released from sensory nerves (Brzozowski *et al*., 2005).

Curcuma longa

Curcuma longa belongs the ginger family (Zingiberaceae). Rhizomes are horizontal underground stems which send out both shoots and roots. It is a typical spice in Vietnam, India and China. The crucial curcuminoid found in *C. longa* is curcumin because of its biological effects. Other curcuminoid compounds found in this herbal are demethoxycurcumin and bisdemethoxycurcumin. In traditional folk medicine *C. longa* has been used treat a variety of ailment, including liver disease, urinary tract infection, wound healing and stomach disorders (Akram *et al*., 2010). Kim *et al*., indicated that compounds extracted from *C. longa* have the ability to inhibit gastric acid secretion by preventing H2-histamine receptors by a competitive mechanism in rat models. (Kim *et al*., 2005). In addition, many studies also showed curcumin has gastroprotective properties, as evidenced by a decreases in total acid production, pepsin activity in gastric juice extra mucosal and reduce ulcer index. (Morsy & El-Moselhy, 2013; Thong-Ngam *et al*., 2012).

Garlic

Garlic, known as *Allium sativum* is one of the oldest cultivated crops in many countries including Vietnam, China and India. Garlic has various compounds like alliin, allixin, amides, 1,2-vinyldithiin, flavonoids, nitrogen, S-allyl-cysteine, phenolic compounds oxides, saponins and sapogenins, thiosulfinates and proteins. In which organosulfur compounds play an important role because they highly contribute to the effective bioactive properties of garlic (Martins *et al*., 2016). This herbal has a reputation as a therapeutic panacea. The aged garlic extract helps to correct histopathological abnormalities in gastric tissue and holds future promise for gastric protection (El-Ashmawy *et al*., 2016). The extract of garlic could effectively promote gastrointestinal motility and promote defecation and improve gastrointestinal function (Chen *et al*., 2018). Moreover, the consumption of garlic potentially modulates the gut microbiota temporarily (Filocamo *et al*., 2012).

CONCLUSION

Medicinal plants have proven effective in alleviating symptoms as well as treating diseases of gastrointestinal diseases. Some chemical compounds such as anthraquinone glycosides, flavonoids, tannins and quercetin have shown strong effects in the gastrointestinal tract. Therefore, a deeper detailed study of medicinal plants to find new compounds with clear activity against gastrointestinal diseases is extremely necessary.

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Chapter 8
Current Status of Commercial Anticancer Phytochemicals and Their Derivatives:
Natural Anticancer Bioactive Compounds

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ABSTRACT

Cancer is one of the most deadly diseases caused due to abnormal division of the cells. Researchers are facing major challenge for finding the effective treatment of the cancer. Various methods of cancer treatment are chemotherapy, surgery, stem cell/bone marrow transplant, radiotherapy, hormone therapy, and anticancer drugs. The anticancer drugs may be natural, semi-synthetic, or synthetic in nature. The most widely used anticancer drugs are the phytochemicals isolated from the plants of their semi-synthetic analogues. So the research focuses on the isolation and identification of the bioactive compounds from natural sources as a potent anticancer agent. However, now the trend has been moved from the natural plant-based products to the natural products mimics of molecule that is the part of human response system. So, the present chapter briefly highlights the current status of commercialized phytochemicals used as anticancer drugs along with mechanism of action of some important drugs.

INTRODUCTION

The pharmaceutical industry is always in search of new lead compounds. The main sources of these

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compounds have been the natural products from different sources that possess different pharmacological important properties. These compounds are very much beneficial for the maintenance of human health. The natural compounds such as aspirin, morphine, digitoxin, quinine and many more are the natural products that have been used for long time for the treatment of various diseases (Cragg *et al.,* 2005). Cancer is one of the diseases which were initially thought as an incurable disease. It is a deadly disease that is characterised by the uncontrolled growth and division of the cells of a part of the body that have started invading the surrounding tissue and then ultimately to the whole body (Cancer Research UK, 2019). Theoretically, there are more than 200 types of cancer but the prominent ones are breast, colon, lungs and prostate cancer. Based on their activity and infection type, cancer has been classified into five classes of brain tumour, carcinoma, leukaemia, lymphoma and sarcoma (Gezici & Sekeroglu, 2019). It is estimated that the global cancer cases will be around 20 million in the next few years (Seca & Pinto, 2018). So the major challenge is the looking for the cancer treatment by investigating new effective anticancer drugs. The currently used treatments for the cancer are radiotherapy, chemotherapy, surgery, bone marrow transplant and using some anticancer drug. The most effective and successful chemotherapeutic and anticancer drugs used for the cancer treatment have been surprisingly natural in origin. The commercialised anticancer drugs can be classified into the synthetic (Chemically synthesised in laboratory), natural (obtained from the natural sources like plants, microbes, marine sources, etc.,), Natural product derivative (include all the semi synthetic analogues of natural products), and natural product mimic (compounds that are similar to natural compounds that are found in humans as the part of their process) (Newman & Cragg, 2020). In actual the most widely used anticancer drugs are either natural products or their analogues that are semi-synthetic in nature (Nahar & Sarkar, 2019). Natural compound shave been used as the basic molecule for the synthesis of analogues for the effective cancer treatment. In fact the natural products are also used to learn about the mechanism of action for the cancer treatment and he same is used for the synthesis of anticancer drugs by doing modifications at specific sites in the basic compounds. These days there is development of the synthetic analogues that are the compounds which mimics the natural compound that is very important for the cancer progression (Kinghorn *et al.,* 2016). The natural products potential for the treatment of cancer was first obliged in 1950 by United States National Cancer Institute which then provided funds to carry out the research related to the identification of the anticancer compounds from the natural sources. After that numerous studies have been carried out to identify the potential anticancer drugs from different natural sources that could be used for the treatment of different cancers. Although initially only natural products were sued for the cancer treatment but with time there has been increase in the use of new approaches for the anticancer drug development that have now overshadowed the potential diversity among the natural products. Among different natural sources, the most widely used are the plants and marine organisms due to their sedentary lifestyle which means they will produce more secondary metabolites to protect themselves from the predators or parasites. This leads to the development of vast diversity among the compounds produced by these organisms as the part of their complex defence system (Williams *et al.,* 1989). Thus these have been the source of many potential therapeutic drugs which have very high specific binding with the potent target (Paul, 1992).

The use of the natural sources for obtaining the compound of interest has been supported well by the following facts. Firstly, the products obtained naturally are synthesised in a combinational manner due to the shuffling of the genes in between different taxa resulting in new combinations that may be beneficial to the mankind (Kingston &Newman, 2002). Secondly, there have been reports of natural products possessing anticancer potential (Shu, 1998; Newman *et al.,* 2000; 2003). Thirdly, the natural products

are very unique and none of these compounds can be artificially synthesised and are not accessible by any other source. Compounds such as halichondrin or paclitaxel can never be synthesised artificially even with the modern combinational chemistry. It is also stated that no artificial compound can ever be same as the natural counterpart structurally or in specificity and there is always diversity among them. Fourth, despite being a non-effective drug, the compounds may act as template for designing of more effective drugs. The compounds have a three-dimensional structure with various ligands on the surface (Henkel *et al.,* 1999). These provide an insight to the protein-protein interactions, which may help the combinational or medicinal chemists to design safe and effective drugs for specific target sites. So this chapter will provide a convenient summary of the commercialised anticancer drugs available which may serve as an inspiration for the scientist of next generation to carry out further research in this area.

PLANT BASED NATURAL ANTICANCER PRODUCTS

Plants are known for synthesising various compounds which may be simple molecules or very complex compounds, for their protection against various biotic and abiotic stresses (Howes, 2018). These plants based chemicals or alternatively known as phytochemicals, have been used since ancient times for the treatment of various ailments including tumours and cancer. Historically the use of plants for the cancer treatment have been reported in 1500 BC but the actual search for the compound which is responsible for the anticancer activity started in 20th century. The modern science has developed tools for the easy accessibility of the plants and their compounds that helped a lot for the identification of the compounds with potential anticancer activity. Plants are not only the source of anticancer drugs, but also provide template for chemical modifications to develop compounds known as analogues that are more effective agents than their natural counterparts (Grothaus *et al.,* 2010). The first and the most successful story of the plant based anticancer drug is the drug paclitaxal, obtained from the bark of *Taxus brevifolia*. The higher plant based anticancer drugs have been classified under four major classes. These classes are Vinca bisindole alkaloids (vincristine, vinflunine, vinorelbine and vinblastine), semi synthetic epi-podophyllotoxins (teniposide, etoposide phosphate and etoposide), taxanes (cabazitaxel, docetaxel and paclitaxel), camptothecin derivative (topotecan and irinotecan). In last two decades, a number of reports have been published related to the plant derived compounds potential as anticancer drugs (Iqbal *et al.,* 2017; Rayan *et al.,* 2017; Lichota & Gwozdzinski, 2018; Khalifa *et al.,* 2019). Mostly the compounds' anticancer potential has been tested in vitro studies against the human cancer cell lines (Mehta *et al.,* 2019; 2021) but a limited have been under clinical trials. A large number of anticancer drugs which are of natural origin or naturally derived have been commercialised (Table 21.1). Some of them have been discussed below.

Camptothecin and its Analogs

The camptothecin is an antineoplastic agent, which has very low solubility in water and has been isolated from the plant *Camptotheca acuminata* extracts (Wall *et al.,* 1966). The compound showed very good activity against the L1210 leukemia but its study was very limited due to its low solubility in water. However it solubility was increased by using its sodium salt, but that resulted in poor activity and increased side effects. Thus its sodium salt was discarded and further study was carried out on the compound (Moertel *et al.,* 1972). Later it was found that the action site for the camptothecin was topoisomerase

Table 1. Commercial Available Natural or Naturally Derived Anticancer Drugs.

Year of Approval	Trade Name	Generic Name
1981	Aclacin	aclarubicin
1981	Pepleo	peplomycin
1983	Celiptium	elliptinium acetate
1984	Farmorubicin	epirubicin HCI
1986	Decapeptyl	triptorelin
1988	Pinorubicin	pirarubicin
1989	Curaderm	solamargines
1989	Navelbine	vinorelbine
1990	Zavedos	idarubicin HCl
1992	Actinex	masoprocol
1992	Nipent	pentostatin
1993	Lentaron	formestane
1993	Leustatin	cladribine
1993	Miltex	miltefosine
1993	Starsaid	cytarabine ocfosfate
1993	Taxol	paclitaxel
1994	Campto	irinotecan HCl
1994	Delivert	angiotensin II
1994	Smancs	zinostatin stimalamer
1995	Taxotere	docetaxel
1996	Etopophos	etoposide phosphate
1996	Hycamptin	topotecan HCl
1999	Agenerase	arglabin
1999	Aromasin	exemestane
1999	Panretin	alitretinoin
1999	Valstar	valrubicin
2000	Levulan	aminolevulinic acid
2000	Mylotarg	gemtuzumab ozogamicin
2001	Metvix	aminolevulinic Me ester
2002	Calsed	amrubicin HCl
2002	Faslodex	fulvestrant
2003	Lipusu	paclitaxel liposomal
2004	Camtobell	belotecan HCL
2004	Docrised	vapreotide acetate
2004	Hexvix	hexyl aminolevulinate
2004	Laserphyrin	talaporfin sodium
2005	Abraxane	paclitaxel nanoparticles
2007	Genexol-PM	paclitaxel nanoparticles
2007	Ixempra	ixabepilone
2007	Nanoxel	paclitaxel nanoparticles
2007	Toricel	temsirolimus
2007	Yondelis	trabectedin
2009	Folotyn	pralatrexate
2010	Halaven	eribulin
2010	Istodax	romidepsin
2010	Javlor	vinflunine
2010	Jevtana	cabazitaxel
2010	Junovan	mifamurtide
2011	Adcetris	brentuximab vedotin
2011	Zytiga	abiraterone acetate
2012	Ameluz	bf-200 ala
2012	Ceflatonin	homoharringtonine
2012	Kyprolis	carfilzomib
2012	Picato	ingenol mebutate
2013	Kadcyla	trastuzumab emtansine
2015	Stakel	padeliporfin potassium
2017	Besponsa	inotuzumab ozogamicin
2017	Mundesine	forodesine HCl
2017	Rydapt	midostaurin
2018	Aplidin	aplidine
2019	Polivy	polatuzumab vedotin

I, which leads to detailed investigation behind its mechanism of action. Now a day's its water soluble semi synthetic analogues topotecan (Hycamtin) and irinotecan (Camptosar) are used for the treatment of solid tumours. Further, various new analogues developed by using the combinational techniques are under clinical trials (Rahier *et al.,* 2005).

Topotecan

Topotecan (Hycamtin, GlaxoSmithKline) approved in 1996 by U.S. FDA, is a semi synthetic analogue of camptothecin. The compound was made water soluble by the addition of basic *N*, *N*-dimethyl-amino-methyl functional group at C9. The compound was marked as miracle for the treatment of advanced ovarian cancer where chemotherapy with paclitaxel and platinum based chemotherapy were failed. Apart from the use for the ovarian cancer, the drug has also been approved for the treatment of recurrent small cell lung cancer. The administration of the drug in human is intravenously and it lack accumulation in the body due to its short half-life. Moreover its affinity towards the blood proteins is also very low compared to other compounds of this class. The side-effects associated with the use of this drug are neutropenia as main toxicity and thrombocytopenia to less extent. Apart from its use in the treatment of ovarian and lung cancer, the drug has also shown promising results against haematological malignancies. The use of topotecan for developing combinational regimes with other drugs such as cyclophosphamide, cytarabine, cisplatin, etoposide, and paclitaxelis is under development (Ulukan & Swaan, 2002).

Irinotecan

Irinotecan (Camptosar, Pfizer) approved in 2000 by U.S. FDA, is a semi synthetic analogue of camptothecin. The compound was made water soluble by the addition of the potent 7-ethyl-10-hydroxycamptothecin analog SN 38. The drug also has a basic bispiperidine on the 10-hydroxy position, which is cleaved in the liver by the enzyme carboxyl-esterase that produces SN-38. This enzymatic activity product is an active compound that is a very potent drug having about 1000-fold more topoisomerase I inhibition activity *in vitro* than the drug, irinotecan itself. Irinotecan has been used for the treatment of advanced colorectal cancer. The drug can be used alone as first line therapy or may be employed in combination with 5-fluorouracil for the treatment. The mode of administration for the dug is intravenously and stays in the body for a longer duration in its lactone form thus increasing its pharmacological importance. The specificity of the irinotecan (lactone form) and SN-38, with the serum albumin results in increased stay of the drug in body. The side-effects associated with the use of drug are limited to diarrhoea and in some cases neutropenia. Besides the activity of the drug against the colorectal cancer, the drug also showed promising results against the cervical, ovarian and lung cancer along with malignant gliomas as evident in the recent clinical trials. Further studies are being carried out to know the effect of combinational therapies along with other drugs like vinca alkaloids, anthracyclines and taxanes (Garcin-Carbonero & Supico, 2002).

Homoharringtonine and Related Compounds

The genus *Cephalotaxus* has been used by the Chinese in their traditional medicinal system for treatment of various ailments. The bark of these Asiatic origins, evergreen trees and shrubs contain various phytochemicals with pharmacological important properties (Huang *et al.,* 1983). More than 20 differ-

ent alkaloids have been isolated from the genus which has been grouped into three categories based on their functional side chain (Takano *et al.,* 1996a; 1996b; 1996c; 1996d; 1996e; 1997). One group has a carboxyl group at the end of the chain and the compounds in this group are3¢*S*-hydroxy-5¢-des-*O*-methylharringtonine, 5¢-des-*O*-methylisoharringtonine, 5¢-des-*O*-methylhomoharringtonine, and5¢-des-*O*-methylharringtonine. The other group has varied number of methyl groups and the members of this group are bishomodeoxyharringtonine, homodeoxyharringtonine, and nordeoxyharringtonine. And the third group contains aromatic rings at the terminal positions of the side chain and the members of the group are 3*S*-hydroxyneoharringtonine, homoneoharringtonine and neoharringtonine. Studies suggested that the bark of *Cephalotaxus fortunei Hook. F* possesses many alkaloids that have antitumor properties. Another species of the same genus, *C. harringtonia* K. Koch, contains an active alkaloid Homoharringtonine (cephalotaxine-4-methyl-2-hydroxy-4-methylpentyl-butanedioate) in its alcoholic fraction which is one of the members of *Cephalotaxus* alkaloids (Grem *et al.,* 1988). Different species contain different alkaloids of the same class with cephalotaxime being their parent compound. Initially the cephalotaxime was isolated from two different species of the genus *Cephalotaxus*, whose structure was revealed later using the x-ray crystallography by using the compound cephalotaxime methiodide (Abraham *et al.,* 1969). Cephalotaxime and its derivatives have a common and unique ring system. Thought the compound cephalotaxime does not exhibit any anticancer potential, but its derived esters are of significant interest due to potent anticancer potential. The most potent anticancer agents that are the analogues of the compound cephalotaxime are homoharringtonine and harringtonine along with other ester derivative, deoxyharringtonine and isoharringtonine (Powell *et al.,* 1970). The clinical trials of the homoharringtonine for its anticancer activity were conducted at the National cancer institute in Bethesda, Maryland. The main issues associated with the use of this drug for cancer treatment is side-effects related with its use. Further study is going on the analogues that are associated with the main drug homoharringtonine (Itokawa *et al.,* 2005).

Podophyllotoxins and Analogs

Podophyllotoxins are the non-alkaloid lignans that have been isolated from different parts of the *Podophyllum* plants. The analysis of podophyllotoxin biologically was followed by inventing its mode of action and opened gates for synthesizing etoposide and teniposide (anticancer drugs). This research demonstrated the interesting development of useful anticancer drugs using natural compounds by chemical alteration. The structural variation in podophyllotoxin resulted in modification of action mechanism is specifically different approach. At present, many new analogs of podophyllotoxin had been reported as potential anticancer drugs. Many recent literatures had various comprehensive updates regarding this compound class (Lee & Xiao, 2005).

The study on *Podophyllum* plants to podophyllotoxin and then to etoposide and teniposide was in continuation for more than a century which resulted in flourishing development of useful drugs using natural sources. The researchers had described this complex path retrospectively (Stähelin & von Wartburg, 1991). In the early 1950s, scientists in Sandoz, Ltd. supposed that, in comparison to cardiac glycosides, podophyllotoxin glycosides might deliver pharmacological profiles that were superior to the aglycone. This assumption encouraged broad efforts to attain both natural and synthesized *Podophyllum* glycosides and in 1963, led to the expansion and commercialization of SP-G (condensation product of the crude *Podophyllum* glycoside fraction with benzaldehyde). SP-G was used to isolate a highly active "antileukemia factor" in minor quantity (<0.25%). Cell proliferation was significantly inhibited by this

component at a low dose *in vitro* and prolonged the survival time of leukemic mice considerably. It had the unique structural features of a free phenolic hydroxyl group at C 4¢ and an epi configuration at C4 and was identified as 4¢-*O*-demethyl-epipodophyllotoxin benzylidene β-Dglucoside (DEPBG). Successive synthetic work to condense 4¢-*O*-demethylepipodophyllotoxin glucoside (DEPG) with various aldehydes and ketones resulted to the discovery of etoposide and teniposide in the latze 1960s (Stähelin & von Wartburg, 1991). In 1983, the FDA approved etoposide for the treatment of testicular cancer, and in 1992, teniposide was brought into the U.S. market. Variety of cancers including small cell lung cancer, testicular cancer, lymphoma, leukemia, and Kaposi's sarcoma are currently treated using these drugs (O'Dwyer *et al*., 1985).

Taxol and Its Analogs

No naturally known anticancer compound had a stronger effect in cure of cancer than Taxol® also known as paclitaxel. Beside its well-known use as anticancer drug in treatment of breast cancer and ovarian cancers and having a several analogs at clinical trials, Taxol never became a drug at all till now. Discovery and development of taxol along with description of its synthesis, medicinal chemistry, interaction with tubulin and its relationship with compounds having same action mechanism such as the epothilones and discodermolide were briefly covered in this review.

On August 21, 1962, Dr. Arthur Barclay from U.S. Department of Agriculture, led a team of botanists working on contract from National Cancer Institute (NCI) began the story of taxol by collecting *Taxus brevifolia* Nutt. Samples in the Gifford Pinchot National Forest in Washington state. At that Time, extraction from samples was done by the Wisconsin Alumni Research Foundation contract laboratory, and cytotoxicity test to KB cells (human epidermoid carcinoma of the nasopharynx) was performed by Microbial Associates in Bethesda, Maryland. Bark and stem extract samples gave positive results and were assigned under a contract from NCI to Dr. Monroe Wall working at newly established Research Triangle Institute in North Carolina and work progressed slowly. This work was organised in parts because of structural complexity and secondly that another compound, camptothecin was under investigation which had consumed much of his resources in Wall's Lab. Dr. Wall in 1971, with his collaborators Dr. Mansukh Wani and Dr. Andrew McPhail, demonstrated the structure of the major active constituent of *T. brevifolia* as taxol, which had been trademarked by a French company for an unrelated laxative product which was later attained by Bristol-Myers Squibb (BMS) who later applied for drug formulation (Wani *et al*., 1971). The chemical compound of was assigned with generic name 'paclitaxel'. The name taxol was retained for compound with no infringement of BMS trademark. Selecting *T. brevifolia* as a source of taxol was very fortunate because it contained only low amount of toxic alkaloids taxine A and B (Itokawa, 2003). very few species had been investigated for probable fractionation leading to isolation of cytotoxic constituents (taxines) and presence of taxol in smaller amount in other species might had remained undetected.

For several decades, a major role in cancer chemotherapy had been played by Paclitaxel (taxol). Monroe E. Wall and Mansukh C. Wani used the bark of Taxus brevifolia (Northwest Pacific Yew Tree) earlier to isolate taxol in 1967. A complex diterpene having a ring of taxane attached with a four-membered ring of oxetane and at C-13 position, an ester side chain is also attached.

Taxotere

Another taxoid drug currently used for clinical purpose and historical section would not be completed without accounting its discovery was docetaxel (Taxotere). In the early 1980s, the Potier group in Paris working at the Centre National de la Recherche Scientifique showed interest in taxol and a series of experiments were carried out for its isolation and semisynthetic studies. As studied earlier, significant initial research was that good yield of the taxol precursor 10-deacetylbaccatin III could be obtained from the needles of *T. baccata* (Denis *et al*., 1988). For semisynthetic studies of taxol from 10- deacetylbaccatin III, the group developed various approaches on the basis of availability of this compound. The first approach involved hydroxyamination of a cinnamoyl substituted baccatin III derivative that resulted in a mixture of stereo- and regioisomeric hydroxyamines (Guèritte-Voegelein *et al*., 1986). It showed excellent activity slightly more than taxol in some tests and thus developed as an equivalent drug to taxol. Taxotere, had gone under phase-I trials in 1993 and in 1996, it was approved for healing of advanced breast cancer and in 1999, it was approved for non-small cell lung cancer and was generically named as docetaxel.

Pro-drugs of Taxol

A major drawback of taxol was its low water-solubility in its earlier development, so developing water soluble pro-drugs was important work on the drug. In a recent survey of taxanes, the only pro-drug in development is T-3782 (Yamaguchi *et al*., 1999). Initial studies focused on 2-position simple ester derivatives because these were rapidly hydrolyzed to taxol. Various succinate and glutarate derivatives (Magri & Kingston, 1988; Deutsch *et al*., 1989), as well as sulfonic acid salt (Zhao *et al*., 1991) and amino acid derivatives were prepared (Magri & Kingston, 1988; Mathew *et al*., 1992). These general types of prodrugs have been noted above but they were having a modified side chain substituent as well as the amino acid attached with a glycolate spacer. As phosphatases were already present in cells, Phosphate prodrugs attracted more interest and this fact was ingeniously used in synthesizing new prodrugs with stability in water but taxol was released by dephosphorylation by phosphatases followed by internal lactonization (Ueda *et al*., 1993). Unfortunately, its binding with plasma proteins and deemed unsuitable to be used as prodrug, beside this it showed better activity against the murine M109 tumor *in vitro* (Ueda *et al*., 1993). Another ingenious approach for the solution to water solubility drawback was developed by showing that migration of 2¢-benzoyl-3 ¢N-debenzoyltaxol from O-benzoyl to N-benzoyl was slow at pH 4.0. it was found that solubility of this compound was more than taxol at this particular pH and under physiological conditions, it can be used as prodrug by converting it into taxol occurring relatively quickly (tò = 15 min) (Hayashi *et al*., 2003). Similar process was applied to develop a prodrug of canadensol. Presently, taxol and docetaxel are the taxane drugs that are used to treat breast, lung, and ovarian carcinomas and also for AIDS-related Kaposi's sarcoma. Taxanes were proved to be most effective agents for treatment of advanced metastatic breast cancer (Rowinsky, 1997) but their benefits for treating breast cancer at early stage had been evaluated recently. Two major reviews elaborated their value recently. One stated, "Evidence of improved outcomes for patients with breast cancer had cleared the addition of taxanes to standard adjuvant regimens," (Hudis, 2003) and other systematic review for treating early breast cancer accounting taxane versus nontaxane concluded, "The results supported that taxanes can be used as adjuvant chemotherapy for women suffering from early stage breast cancer involving lymph nodes." It was refractory to primary chemotherapy that docetaxel was the choice of drug for treating advanced non–small cell lung cancer (Kris & Manegold, 2001). No significant difference was

seen in the response rates and survival on comparing the efficacy of three different regimens (cisplatin and docetaxel, cisplatin and gemcitabine, or carboplatin and taxol) (Levin, 2001). The significance of taxol was firstly discovered as an anticancer drug for ovarian cancer and still it is a main target. In the early findings of a European–Canadian study, the regimen of cyclophosphamide–cisplatin used previously was found inferior to the combination of taxol–cisplatin (Piccart *et al*., 2000) and also confirmed as the standard of care in women with advanced ovarian cancer. Taxanes were not to be considered as wonder drugs, they had nevertheless brought significant benefits to most of the cancer patients. The recent studies of successful phase III trial done using albumin nanoparticle based formulations of taxol ABI-007 showed that enhanced formulations could have significant effect (Garber, 2004). In metastatic breast cancer patients, the overall response rate for ABI-007 was 33% that was much better than taxol i.e. 19%. Thus, it is clear that in Twenty-first century, taxols and its analogs would be going to play significant role in cancer chemotherapy.

MECHANISM OF ACTION

Numerous phytochemicals have been used for the treatment of different cancers and a lot are under the clinical trials. However, the mechanism of action of these phytochemicals varies greatly. The mode of their action may be inside the cell or outside and they are very specific in their action (Figure 21.1). A brief about the some mechanism of action like enzyme inhibition, cell cycle arrest, macromolecule binding etc., have been discussed below.

Enzymes Inhibition

Topoisomerases I or II

Gossypol, known for its potency as male contraceptive, was isolated from the cotton plant. The action of the compound against the cancer cell lines (mammary adenocarcinoma, Ehrlich's ascites carcinoma and ulcerated melanoma) leads to curiosity to know the mechanism of action behind its anticancer potential (Adlakha *et al.,* 1989). The results showed that the compound exhibits the anticancer potential by a unique mechanism by interacting with the topoisomerase II resulting in its decreased DNA cleavage activity (Adlakha *et al.,* 1989). Further investigation lead to the discovery of two different ligand-topoisomerase complexes. One class of the complex helps in the stabilisation of the DNA-topoisomerase complex thus inducing the DNA breaks while the other class ligands do not induce ant DNA breaks but interfere with the catalytic activity of the topoisomerase. The study reported that the gossypol compounds acts as the second class ligand where the DNA-topoisomerase interaction is blocked without DNA breaking (Senarisoy *et al.,* 2013). The anticancer compound camptothecin also works with the same mechanism as topoisomerase inhibition along with some effects on the DNA. It had shown its anticancer activity against the cultured human keratinocytes as well as in mouse model (Lin *et al.,* 1999). Another compound (-)-epicatechin-3-O-gallate (EGCG), an important catechin found in the tea, showed the inhibition potential against the topoisomerase I but with varied response depending upon its source. It does not show the inhibitory potential against the cancerous cell (COLO 201, HeLa and A549 cells) topoisomerases but very strong activity against the vero cells, calf thymus gland cells and wheat germ cells' topoisomerases. The inhibitory potential of the compound can be altered by substitution of the functional groups with

other groups. One of the example is gallic acid substitution at the 3 position significantly amplified the activity against the human placenta topoisomerase II. Similarly, the hydroxyl group substitution at the 39 position enhanced the activity in similar way but against the topoisomerase I (Suzuki *et al.,* 2001). Another compound GAX46 isolated from *Ganoderma amboinense* sensitized the cell towards their apoptosis by its topoisomerase I &II inhibitory potential in HuH-7 cells (Li *et al.,* 2005).

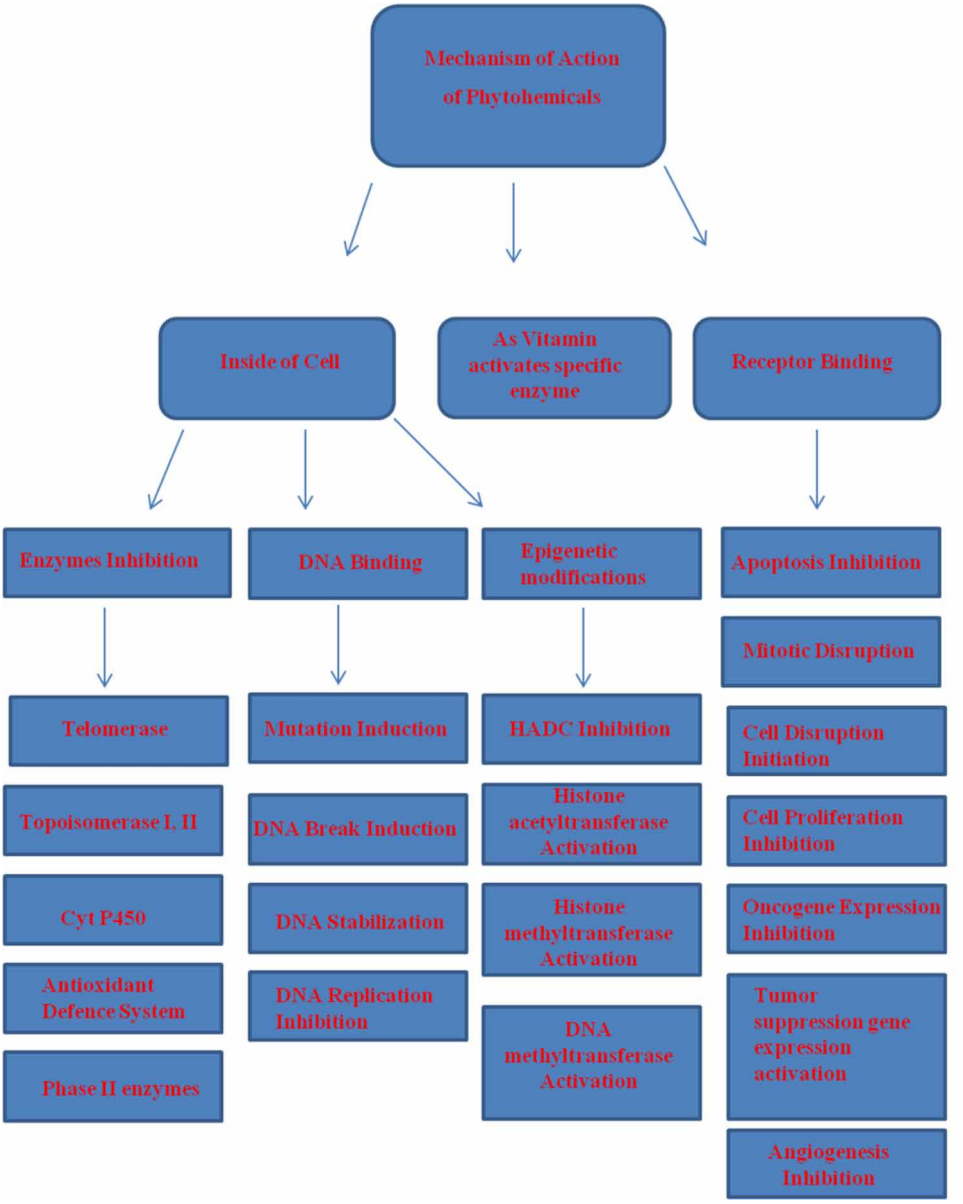
Telomerase

Telomerase are the eukaryotic enzymes that have the reverse transcriptase activity and are formed of different components such as RNA, proteins (p95 & p80) and reverse transcriptase motif (p133). The enzyme is very much essential for the cell division activity (Collins & Gandhi, 1998). The activity of the telomerase has been compromised by the EGCG thus inhibiting the proliferation of the colon adenocarcinoma (HT290) and monoblastoid leukemia (U937) cells. The inhibitory potential against the telomerase has been checked both in vivo and in cell free system. Additionally the ECGC at non-toxic concentration resulted in chromosomal abnormalities and short telomeres which resulted in limiting the cell life span (Naasani *et al.,* 1998). Another study reported that ECGC results in the prevention and apoptosis of telomerase activity thus helps in the prevention of the cervical cancer carcinogenesis. These effects of the ECGC are supposed to be happening in the early stages of cervical lesions (Yokoyama *et al.,* 2004). The EGCG exposure to the cells can result in decreased proliferation along with induction of the apoptosis in the breast cancer cells (MCF-7). The action of the compound was supposed to be due to the decreased expression of the hTERT or human telomerase reverse transcriptase (Berletch *et al.,* 2006). Camptothecin also showed the apoptotic effect in the HL-60 cells. It was reported that the effect of the compound was due to decreased telomere activity in a time dependent manner. The expression of other components associated with the telomerase was also studied and no significant different in the expression pattern was reported for the telomerase associated protein I (TLP1), hTERT and human telomerase RNA, after the exposure to the camptothesis. However a significant decrease in the expression of the Bcl-2 was reported which was supposed to be responsible for the compounds activity. The camptotehcin induce the apoptosis of the cell without disturbing the RNP complex associated genes expression (Jiang *et al.,* 2000). The telomerase inhibitory effect of the camptothecin has also reported in human keratinocytes HaCa T-cells which resulted in the inhibition of proliferation resulting in cell apoptosis. This action was found associated with the telomerase activity down regulation (Liu *et al.,* 2006). An analogue of the camptothecis that is isocamptothecin also exhibited the same effect on the HaCa T-cells (Lin *et al.,* 2008). A high dose of crocin also resulted in the growth inhibition of the cancer cell lines which ultimately lead to the apoptosis. The therapeutic study on the saffron compounds including crocin showed that these compounds interact with the telomerase-DNA structures along with the i-motif and G-quadruplex (Hoshyar *et al.,* 2012; Khosrojerdi *et al.,* 2012; Noureini & Wink, 2012).

Other Enzymes

Apart from the telomerase and topoisomerases, the compounds inhibit the cancer cell proliferation by affecting other enzymes such as VEGF49, MMP48-2 and -9. By affecting the expression of these enzymes, the invasion and migration of the human lung cancer cell line (A549) has been inhibited by the curcumin (Lin *et al.,* 2009).

Figure 1. Different mechanism of action of the phytochemicals for the cancer management.



Direct Binding to Bio-macromolecules

The cellular process can be altered by binding of the phytochemicals with biomolecules like proteins, DNA and microtubules. Paclitaxal, a derivative of taxol that has been in use as an effective chemotherapeutic compound is very unique in its functioning. The compound acts by stabilizing the microtubule assembly against the depolymerisation process by binding with it even in the absence of proteins and GTP50. The in vitro study revealed that the compound binds with the microtubule β-subunit and produce parallel rays after polymerisation. The mechanism of action is in contrast with the cochicine which inhibit the

formation of microtubules. Paclitaxel at high dose hold back the detachment from the centrosomes thus blocks the cell cycle in the G2/M phase (Horwitz, 1994; Priyadarshini & Keerthi, 2012).

Numerous phytochemicals such as delphinidin, kaempferol, quercetin, crocetin, crocin, genistein and resveratrol, act by direct binding with the DNA (Usha *et al.,* 2005; Kanakis *et al.,* 2005; 2009; Bathaie *et al.,* 2007; Gatz & Wiesmuller 2008). However the exact mechanism of their action is not clear but these are known to protect the nucleic acids from the damage caused due to oxidative stress. However the role of resveratrol is quite antagonistic and it has been reported to break the DNA in presence of copper ions along with inhibiting the action of DNA polymerases α and δ. Despite the presence of antioxidant potential, the low concentration of the resveratrol has been reported to possess carcinogenic effect as studied in mice (Sgambato *et al.,* 2001).

RNA Modulation

MicroRNAs (miRNAs) are 19-25 nucleotides long non-coding RNAs which have been found to actively involved in regulation of gene expression. The cancer initiation and progression has been reported to be associated with the miRNA deregulation. Later it was reported that the mRNA function is post-transcriptionally regulated by miRNAs. The miRNAs could act as both effectors and targets in gene silencing and hypermethylation as evident for a study on human cancer (Liao *et al*., 2013). The effect of curcumin in the modulation of the miRNAs has been reported by several workers in different cancer cell lines (Yu *et al*., 2010; Fang *et al*., 2011; Liang et *al*., 2012; Liao & Leung, 2013). The down regulation of the miR-186* miRNA by the curcumin is thought to be the mechanism behind the anticancer property of the compound against A549/DDP59 cell lines. Addition of the miR-186* inhibitor in the A549/DDP cells have been reported to induce apoptosis while miR-186* over expression inhibited the apoptosis induced by curcumin significantly confirming the miR-186* requirement for the cancer progression along with the effectiveness of curcumin for the lung cancer management (Yang *et al*., 2013). The miRNAs expression in the gemcitabine resistance and sensitive PC62 cells were compared along with the effect if isoflavone and DIM63 on miRNAs expression. It was reported that the resistant cells have lower expression levels of the miRNAs. The treatment of resistant cells with either isoflavone or DIM resulted in the morphological changes consistent with the epithelial cells, which indicated the mesenchymal-to-epithelial transition showing the role of the compounds in the regulation of miRNA involved in phenotypic expression (Lin *et al*., 2012). Curcumin has also been reported to alter the miRNA expression leading to the sensitization of the chemo-resistance cancer cells which might be associated with the epithelial-mesenchymal transition (EMT) in some cancer cells (Sondhi *et al*., 2010; Pergola *et al*., 2012). Other chemicals that could affect the EMT by regulating the miRNA are EGCG and I3C67 (Pathania *et al*., 2014).

Autophagy and Unfolded Protein Response (UPR)

The two cellular responses autophagy and UPR shows alteration against environmental factors that affect a cell's survival or death. These factors are accompanying with the proteasomal degradation and cellular pathways that degrade and recycle excess or damaged proteins to maintain cellular homeostasis and life. In response to nutrient depletion, autophagy was discovered as a survival signal for the degradation of cellular components. The UPR, on the other hand, starts when the ER detects an overabundance of unfolded proteins. Autophagy can be initiated to alleviate damage and stress when proteasome function

and/or UPR induction (due to ER stress) are insufficient. If this network of processes is unable to repair the damage or overcome the stress, the cell is killed by apoptosis (Lee *et al.,* 2009; Benbrook, 2012). In recent clinical trials, the combination of autophagy suppressors with apoptosis inducers has been examined (Benbrook, 2012). However, further research is needed to determine how utilising phytochemicals in cancer therapy affects autophagy, proteasomal degradation, UPR, and apoptosis. Autophagy has been classified as type II programmed cell death, and its induction has been studied in the presence of certain phytochemicals. For example curcumin has been found in both in vitro and in vivo investigations to block the Akt/mTOR/p70S6K pathway and activate the ERK1/2 pathway, resulting in the induction of autophagy in malignant glioma. Curcumin causes differentiation in glioma-initiating cells in vivo and in vitro through triggering autophagy, which was discovered several years later (Zhuang *et al.,* 2012). Curcumin stimulates autophagy in A54969 cells by activating the AMPK70 signalling pathway, according to later research (Xiao *et al.,* 2013). The effects of taxol have been examined in MDA-MB-231 and T47D breast cancer cells. Taxol promoted UPR and ATF4 activation (the latter in connection with hypoxia-induced genes) and was implicated in taxol-induced autophagy completion, according to the findings (Notte *et al.,* 2015).

Apoptosis Induction

Apoptosis is a type of programmed cell death that occurs naturally (genetically) in some cells (other forms include autophagy and necroptosis). Caspases (cysteine-rich aspartic acid-containing proteases) catalyse this self-destruction process to destroy cells with a short life span (such as erythrocytes), cells that are unneeded (such as the separation of fingers and toes in a growing human embryo), and cells that are damaged. The presence of a stimulus or the removal of a suppressing signal activates it. Excessive apoptosis leads to atrophy and neurological diseases, whereas insufficient apoptosis leads to excessive cell growth, which can lead to cancer. Apoptosis is promoted by activation of extracellular or intracellular death signals via Fas and Bax, respectively, although Bcl-2 opposes it. Death receptors are members of the TNFR71 family and have an intracellular death domain. P53 is a key activator of the intrinsic pathway and a sensor of cellular stress. Antiapoptotic signal NF-B72 can be triggered by growth factor receptors. In cancer and other disorders, targeting apoptotic pathways with phytochemicals, medicines, and other methods is a therapeutic goal. Using an in vivo strategy in which 4T1 cells were transplanted subcutaneously in Balb/c mice, the effects of dietary GSPs73 were investigated. In the tumour microenvironment, dietary GSPs (0.2 percent and 0.5 percent, w/w) significantly reduced the development of implanted 4T1 tumour cells and increased the Bax/Bcl-2 ratio, released cytochrome c, stimulated Apaf-1, and activated caspase-3 (Livraghi *et al.,* 2003). Saffron extract has been shown to induce apoptosis in MCF-7 breast cancer cells. The mechanism involved the production of the Bax protein and the release of caspases (Mousavi *et al.,* 2009). Crocin, a carotenoid derived from saffron, was found to be responsible for apoptosis induction in animal models of gastric cancer and AGS cells. The Bax/Bcl-2 ratio and caspases both increased significantly, according to the findings (Martel et al., 2008). Crocetin inhibited gastric cancer growth in AGS (Bathaie *et al.,* 2013) and BGC-823 (He *et al.,* 2014) gastric cancer cells by inducing apoptosis, cytochrome c, and caspase release, and raising the Bax/Bcl-2 ratio.

Inhibiting Angiogenesis

The progression of the tumor is very much dependent on the angiogenesis due to the demand of high amount of oxygen during the growth of the tumor. The process of uptake of nutrients and elimination of the wastes is done simply by the diffusion process but during speedy growth there is deficiency of the nutrients in the micro-environment of the tumor. This leads to the expression of the vascular epithelial growth factor (VEGF) by the tumor cell which is required for the process of angiogenesis. Thus one can control the growth of the tumor by controlling the angiogenesis. Various plant extracts have been reported to exhibit the anti-angiogenic effect which could be used for controlling the tumour growth by inhibiting the angiogenesis (Sagar *et al.,* 2006). Different compounds such as querticin, curcumin, resveratol, EGCG, aloe vera, ginger, etc., have been studied which works by different pathways like direct method by inhibition of VEGF or indirectly by affecting angiogenesis related genes such as c-jun, Src, EGFR, K-ras, Tp53 and so on. The mechanism of action of an alkaloid piperine, isolated from the black pepper is by inhibition of the G(1)/S transition and thus the proliferation of the HUVECs without actual killing of the cells. The inhibitory potential was due to the inhibition of the phosphorylation of Akt. It has been reported that piperine affects various aspects of angiogenic process under both in vivo and in vitro conditions as tested by the MDA-MB-231 induced angiogenesis in chick embryo (Doucette *et al.,* 2013).

CONCLUSION

The plant derived natural products have been used as potential anticancer drugs and is expected to be the potential source of new and more effective drugs. The vast diversity of the plants added by the combinational approach for the product development has led to the infinite number of phytochemical obtained. The synthetic approach for the production of natural compound analogues have also benefitted in the way of increasing the specificity and anticancer activity of the natural compounds. Numerous plant based phytochemicals as well as their analogues are under the clinical trials and are expected to be commercialised soon. The demand of time is not to restrict the anticancer agent discovery approach to in vitro studies on the cancer cell lines but to use the collaborative and multidisciplinary approach for the final drug development.

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Chapter 9
Medicinal Plants for the Treatment of Type 2 Diabetes

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ABSTRACT

Type 2 diabetes (T2D) is a metabolic disorder related to persistent hyperglycemia. It is characterized by lack of secretion and/or reduce activity of insulin, which causes many chronic complications. Medicinal plants offer a passel of remedies that resolve symptomatology and mitigate the progression of T2D. Although several pre-clinical and clinical investigations indicate the success of conventional medicine in the prevention and treatment of diabetes, still there are several side effects. Consequently, this necessitates the exploration of complementary and alternative treatment programs that may include natural products as safe and effective anti-diabetic candidates. This chapter reviews the medicinal plants and their bioactive compounds utilized in diabetes therapy and molecular targets of Type 2 diabetes treatment. The authors elucidate present findings and contribute to ongoing investigations into potential alternative therapies for T2D.

INTRODUCTION

Diabetes mellitus, a chronic state of metabolic diseases, is caused by deficiency of insulin secretion and insulin activity. There are three primary types of the disease: Type 1 diabetes (T1D), Type 2 diabetes (T2D) and Gestational diabetes (GD). Of the three, Type 2 diabetes or non-insulin dependent diabetes (NIDDM) is the most prevalent form of this disorder in the world (Jin *et al.,* 2019). The preponderance of this pathology is projected to significantly increase from 285 million (9.3%) in 2019 to 578 million (10.2%) in 2030 and 700 million (10.9%) in 2045 (Federation, 2019). Although the main risk factors for T2D are obesity, age, family history, hypercaloric diets and inactive lifestyle, the effect of this disease on non-obese and physically active people is fundamental in determining an onset mechanism (Ferhati *et*

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al., 2019). The stable levels of glucose are maintained by a complicated mechanism containing hepatic glycogenolysis and gluconeogenesis. After a meal, pancreatic β-cells secrete insulin preventing hepatic glucose output and stimulating the glucose absorption into peripheral tissues (Alvim *et al.,* 2015). The World Health Organization has suggested that the oral glucose tolerance test (OGTT) is designed for the diagnostic criteria of diabetes with fasting glucose 7.0 mmol/L or more. In addition, the expert committee of the American Diabetes Association recommended a cut-point for the diagnostic criteria at 6.5% or more of HbA1c level (Forouhi & Wareham, 2010). The aim of these therapeutic options is to maintain patient blood glucose levels close to physiological range and to prevent serious symptoms as well as late complications in the long term. The antidiabetic therapy currently contains oral drugs reducing hyperglycaemia and exogenous insulin injection as a last method (Ferhati *et al.,* 2019). This book chapter will focus on proposing or determining a mechanism of action for antidiabetic agents employed in the treatment of T2D.

MOLECULAR MECHANISM OF TYPE 2 DIABETES TREATMENT

AMP-Activated Protein Kinase (AMPK)

The AMPK heterotrimeric complex contains α-catalytic subunit with β and γ-regulatory subunits. Twelve different AMPK molecules are comprised of four isoforms of α and β subunits (α_1, α_2, β_1,β_2) and three isoforms of γ subunit (γ_1, γ_2, γ_3) (Alvim *et al.,* 2015). Recent studies show the important role of AMPK in glucose uptake with in muscle cells in T2D patients. After the skeletal muscles contract, the glucose uptake is prompted by increasing AMP/ATP ratio and decreasing creatine/phosphocreatine ratio. The levels of AMP increase significantly leading to AMPK activation via residual threonine phosphorylation (Thr^{172}) in the α-subunit by LKBI (upstream serine-threonine kinase) (Alvim *et al.,* 2015). Another study also reported that AMPK activated by metformin based on the interaction between AMPK, LKBI and axin in liver *in vivo*, HEK (Human embryonic kidney)-293 cells and embryonic fibroblasts of mouse (Carling, 2017). The 5- aminoimidazole-4-carboxamide-1-β-D-ribonucleoside (AICAR) activation is similar to AMP affecting AMPK. *In vitro* studies suggested that the glucose transport was increased considerably by exposing to AICAR of rat muscles cells (Alvim *et al.,* 2015).

The decrease in cold stimulated glucose uptake into brown-adipose tissue (BAT) as well as adipose tissue AMPK was exhibited at obese and T2D patients. White adipose tissue (WAT) is known as a storage repository and endocrine organ, in contrast, BAT can preserve thermal homeostasis via the dissipation of large amount of energy in the heat-form. Many persuasive evidences have showed that AMPK regulated the BAT development, preservation of mitochondrial activity of BAT and browning of WAT. In addition, the activation of APMK in muscle and liver increases fatty acid uptake, oxidation and repress lipid and cholesterol accumulation towards the therapeutic benefit in T2D people (Desjardins & Steinberg, 2018). T2D treatments with metformin, the sodium glucose cotransporter-2-inhibition (SGT2i) such as canagliflozin drug increase significantly AMPK activation in the liver by restraining mitochondrial function. Various natural products that decreased hyperglycaemia such as quercetin, berberine and resveratrol also stimulate AMPK via mitochondrial function (Desjardins & Steinberg, 2018).

Protein tyrosine phosphatase 1B (PTP1B)

The superfamily of protein tyrosine phosphatases (PTPs) and protein tyrosine kinases (PTKs) has a regulatory capacity for insulin and leptin signaling pathways via transfer of phosphate groups from specific tyrosine (Tyr) residues or addition of phosphate groups to Tyr. Hence, PTPs and PTKs are involved in T2D by the coordinated action as potential targets (Jänne *et al.,* 2009).

PTP1B is a non-transmembrane protein tyrosine- phosphatase associated with negative modulating insulin and leptin signaling in the cells. It is capable of the dephosphorylation of the activated insulin receptor (IR) and the IR substrates after autophosphorylating several tyrosine residues on the intracellular kinase domain of IR-β subunit (Jin *et al.,* 2019). PTP1B and T cell protein-tyrosine phosphatase (TCPTP) were deleted in the hypothalami of obese mice leading to improve leptin and insulin sensitivity, suppress feeding and enhance browning to reduce adiposity and increase glucose metabolism (Dodd *et al.,* 2019). A *vivo* assay has reported that 5'-AMP (pAMP) was promoted in plasma of obese diabetic mice and exogenous 5'-AMP induced hyperglyceamia as T2D in wild mice. In addition, these adenine nucleotides also associate with the activity of PTP1B in type 2 diabetes (Yang *et al.,* 2019).

α- Glucosidase

α-glucosidase, an enzyme at intestinal brush border, is responsible for hydrolysis of disaccharides. Inhibition of α-glucosidase induces to poor and slow absorption of carbohydrates and lead to blood glucose reduction after a meal. In addition, this inhibition may also promote the liberation of glucagon like peptide-1 which may increase to their effects on blood glucose levels (Health, 2017). α-glucosidase inhibitors (AGIs) were recommended as efficiently first-line agents or in combination with other drugs for T2D treatment. However, some studies have reported that the use of AGIs induced various unusual adverse hepatic cases and increase of liver function impairment was exhibited in patients using acarbose compared to patients without this drug. Moreover, flatulence, diarrhea, abdominal bloating and discomfort are common side effects of this agents (Inzucchi *et al.,* 2015).

α-Amylase

α-amylase is also a member of α- glucosidase family which is necessary for the hydrolysis of α-1,4-glycosidic bonds in starch, glycogen, oligo and polysaccharides. There are two types of α- amylase in human body: salivary enzymes and pancreatic enzymes, both of them participate in the digestion which produces glucose, maltose and oligo saccharides. These monosaccharides absorbed into the circulation cause an increase of blood glucose level, which is associated with obesity, type 2 diabetes and other metabolic diseases (Boehlke *et al.,* 2015). Human α- amylase is encoded on chromosome 1 as member of a multigene family and the different isozymes are only expressed in the salivary glands as well as pancreas. The *amy* 1 gene encodes the former amylase expressed in the salivary, mammary and lacrimal glands, while the pancreas secrete amylase isozyme encoded by the *amy* 2 gene (Tundis *et al.,* 2010). α-amylases have been widely researched as potential targets for the treatment of T2D. α- amylase inhibition does not base on regulation of hormones like insulin and glibenclamide, whose use in the long term may develop the tolerance of these drugs (Bueno *et al.,* 2019).

Advanced Glycation End Products (AGEs)

Glycation plays an important role in instinctive destruction of cellular and extracellular proteins in living organisms. Advanced glycation end products (AGEs) are proteins and/or lipids becoming glycated and oxidized after constant connection between reducing sugars (e.g., glucose) or short-chain aldehydes (e.g., glycoaldehyde) and amino groups and/or high level of oxidative stress. There are three independent pathways creating AGEs *in vivo*: the Maillard reaction, the Polyol Pathway and the increase of oxidative stress causing the synthesis of a-dicarbonyl compounds such as glycolaldehyde, glyceraldehyde, glyoxal, methylglyoxal and 3-deoxyglucosone. These reactive intermediates can further respond with circulating proteins via a reversible Schiff base and Amadori products leading to additionally form AGEs like glucosepane associated with the mechanism of diabetic complications (Deluyker *et al.,* 2017). The receptor for advanced glycation end products (RAGE) belongs to the superfamily of immunoglobulins known as a multi-ligand transmembrane receptor on several cell types including cardiomyocytes, endothelial cells, macrophages, lymphocytes and ðbroblasts. High-mobility group protein (B)1, Mac-1, amyloid-β-protein, phosphatidylserine and S-100 calcium-binding protein along with AGEs are among the most recognized ligands of RAGE (Sanajou *et al.,* 2018). AGEs-RAGE interaction can generate reactive oxygen species (ROS) by activating nicotinamide adenine dinucleotide phosphate oxidase. ROS cause the alteration of the protein structure and function as well as the impairment of excitation–contraction coupling at the cellular level leading to develop cardiac dysfunction (Hegab *et al.,* 2012). In addition, activation of the AGE-RAGE axis relates to stimulate intracellular oxidative stress formation and activation of NF-κB in vascular wall cells, resulting in promotion of atherosclerosis/inflammation-related gene expression associated with vascular complications in diabetes (Yamagishi *et al.,* 2015). Matsui et al. reported that a RAGE-aptamer abrogated conceivably several diabetes related to renal impairments such as increase in macrophage inðltration, surge of proðbrotic cytokines and proinñammatory as well as activation of AGE-RAGE-oxidative stress axis (Matsui *et al.,* 2017).

Based on above mentioned targets, several antidibetic drugs have been studied and used for T2D patients such as metformin, sulfonylureas, Glinides, SGLT2i, AGIs However, the treatment with these drugs in long term may cause a number of side effects including diarrhea, flatulence, weight again, nausea, especially, risk of hypoglycemic and therefore, we review different natural products as an important alternative source of promising candidates against T2D.

NATURAL PRODUCTS USED FOR THE TREATMENT OF TYPE 2 DIABETES

Salvia Miltiorrhiza Bge.

Salvia miltiorrhiza (Labiatae) known as traditional Chinese medicine has been widely used for the treatment of cerebrovascular diseases- and coronary artery diseases (Huang *et al.,* 2015). The phytochemicals of *S. miltiorrhiza* reveal that it may include hydrophilic and lipophilic compounds such as caffeic acid, isoferulic acid, protocatechuic acid, protocatechuic aldehyde, ferulic acid, rosmarinic acid, dihydrotanshinone I, przewalskin, cryptotanshinone, tanshinone I, tanshinone IIA, salvianolic acid B and salvianolic acid A (Zhong *et al.,* 2009). In a *vivo* study, salvianolic acid B (SalB) has been a beneficial effects on insulin action, glycogen production and activity of antioxidant enzymes, leading to improve the symptoms of diabetes mellitus. According to this study, SalB (100 and 200 mg/kg) significantly in-

hibited hyperglycaemia and enhanced sensitivity of insulin. Furthermore, the significant decrease of total cholesterol, non-esterified fatty acids, hepatic and muscle glycogen as well as the increase of high-density lipoprotein cholesterol were demonstrated in diabetic mice induced by high-fat diet and streptozotocin (Huang *et al.,* 2015). Another polyphenolic compound, Salvianolic acid A (SalA) notably reduced fasting blood glucose, 24-h food and water intake, concurrently enhanced mitochondrial function of hepatic and skeletal muscle tissues. In addition, SalA caused the activation of AMPK phosphorylation via Ca(2+)/calmodulin-dependent protein kinase β (CaMKKβ)/AMPK signaling and independent of liver kinase 1 (LKB1)/AMPK pathways (Qiang *et al.,* 2015). In a mouse model with diabetic nephropathy, *S. miltiorrhiza* extracts ameliorated high levels of 24-h urinary protein excretion and reduced the kidney levels of transforming growth factor β1, monocytes/macrophages and the receptor for RAGE (Lee *et al.,* 2011). Qian et al. (2012) showed that reduction of oxidative stress was induced by a decrease in the production of malondialdehyde at day 30, simultenously increasing the formation of serum glutathione and activity of antioxidant enzymes such as superoxide dismutase, paraoxonase and glutathione reductase at day 60 after administration of *Salvia miltiorrhiza* aqueous extract in T2D patients with chronic heart disorder (Qian *et al.,* 2012).

Punica granatum

An *in vitro* study examining a number of phenolic components in the extracts of whole pomegranate containing seeds, peels, flowers and juice found that they had an ability to decrease carbohydrate digestion enzyme activity. The methanolic flower extract prevented α-amylase and α-glucosidase activity, while the metabolic peel extract and two active compounds (gallic acid, ellagic acid) displayed selective α-glucosidase inhibition (Kam *et al.,* 2013). In another *in vitro* screening assay, the methanolic extract of *P. granatum* rind inhibited three metabolism-related enzymes: hyaluronidase, tyrosinase and α-amylase leading to therapeutic applications in many chronic diseases such as diabetes, hypertension and cancer. The main active compound identified in this extract was quercetin and its inhibitory activities against these enzymes was competitive, un-competitive and non-competitive, respectively (Ahmed *et al.,* 2019). The *P. granatum* seed oil (PSO) also has several bioactive components utilized into controling insulin resistance as well as diet-induced obesity. Three dietary fatty acids isolated from PSO included punicic acid, oleic acid, and linoleic acid, which prevented adipogenesis of human adipose-derived mesenchymal stem cells, improved inflammation, reduced glucose uptake and ATP formation. Furthermore, the study showed that these fatty acids were found to regulate the mRNA expression of the studied obesity-associated gene transcripts (Trichur Khabeer *et al.,* 2019). Banihani et al. (2014) investigated the influence of pomegranate juice (PJ) on fasting serum glucose (FSG) levels and insulin levels in 85 participants with type 2 diabetes. They observed significant decrease of FSG levels, insulin resistance and increase of β-cell function at 3 hours after oral administration of 1.5 mL of PJ, per kg body weight. This effect did not relate to the sex of participants and was less potent in elderly patients (Banihani *et al.,* 2014). These studies suggest that *Punica granatum* extract may be an effective source for the treatment of type 2 diabetes.

Camellia species

Camellia Joponica

Camellia japonica is known as a garden plant whose flowers and seeds have been used for traditional cosmetics in East Asia (Ochiai *et al.,* 2018). Uddin et al. evaluated EtOAc-soluble fruit peel extract from *C. japonica* (Theaceae) for PTP1B inhibition *in vitro.* Four new oleanane-type triterpenes were identified, together with six known components of this class and many of them showed significant effect on PTP1B inhibition with IC_{50} values in the range of 3.77 ± 0.11 to 6.40 ± 0.81 μM (Uddin *et al.,* 2014). In another obese mouse model, rats fed with 1% *C. japonica* seed extract for 53 days showed increased fecal fat excretion as well as a reduction of body weight gain and lipid parameters in the liver and in plasma. Furthermore, they observed a delay of lipid-induced hypertriglyceridemia after a single consumption of *C. japonica* (Ochiai *et al.,* 2018). A study with hypercholesterolemic rat model showed that *C. japonica* fruit extracts have a strong cholesterol-lowering effect caused by a reduction of triglyceride, low-density lipoprotein and serum total cholesterol, as well as an increase in serum high-density lipoprotein. In addition, *C. japonica* fruit extracts decreased lipid peroxidation in plasma by inhibiting the production of thiobarbituric acid reactive substance (TBARS) (Lee *et al.,* 2016). *C. japonica* may be a potent therapeutic option for the improvement of many diseases related to hypercholesterolemia, however, more investigations need to be performed to determine a clear mechanism of action for *C. japonica* in the treatment of T2D.

Camellia sinesis L.O. Kuntze (Green tea)

Deng et al. (2018) showed the ameliorated therapeutic potency of bioactive compounds extracted from green tea in the high fat diet/streptozocin-induced diabetic mice. After oral administration of tea peptides (1000 mg/kg, bw/day) for 5 weeks, rats significantly decreased FSG level, and the amount of creatinine, total urinary protein, and urine nitrogen related to the impairment of glomerular filtration function. The mechanism based on stimulation of the polyol PKCζ/JNK/NF-κB/TNF-α/iNOS and AGEs/RAGE/TGF-β1 pathways, upregulation of podocin expression in the glomeruli as well as decrease in release of pro-inflammatory cytokines (Deng *et al.,* 2018). Hua et al. (2018) evaluated the effects on enzymatic inhibition of the novel acylated flavonol tetraglycoside (camellikaempferoside C, 1), flavone glycosides (FGs), other flavone and flavone glycosides (FGs) identified from *C. sinensis*. The kaempferol monoglycoside inhibited intestinal glucosidase activity with IC_{50} value of 40.02 ± 4.61 μM, while kaempferol diglycoside displayed inhibitory activity against α-amylase with IC_{50} at 0.09 ± 0.02 μM. Molecular docking suggested the interaction of kaempferol monoglycoside with α-glucosidase and kaempferol diglycoside with α-amylase via hydrogen bonding and van der Waals forces led to the quench of intrinsic fluorescence of both enzymes (Hua *et al.,* 2018). A clinical trial of 120 overweight women showed that green tea in the absence of metformin decreased FSG level and enhanced glycaemic control and lipid profile including total cholesterol and LDL-cholesterol. These results suggested that green tea extract could be a promising alternative for reducing risk of T2D in overweight women (Alves Ferreira *et al.,* 2017).

Ludwigia octovalvis (Jacq.) P.H. Raven

Ludwigia octovalvis (Onagraceae) has traditionally been used as a supplemental therapy for the treatment of many diseases such as edema, nephritis, hypotension and diabetes (Lin *et al.,* 2017). The phytochemicals of the herb of *L. octovalvis* contain beta-sitosterol, oleanolic acid, gallic acid, ellagic acid,

quercetin, luteolin, apigenin, tormentic acid, 2-alpha-hydroxy ursolic acid, daucosterol, maltol, methyl brevifolincarboxylate and 3, 4, 8, 9, 10-pentahydroxydibenzo[b, d]pyran-6-one (Yan & Yang, 2005). Morales et al. measured the inhibitory effect on new pancreatic lipase and α-glucosidase of *L. octovalvis* hydroalcoholic extract in comparison with orlistat, acarbose, and a *C. sinensis* hydroalcoholic extract. *L. octovalvis* hydroalcoholic extract and its ethyl acetate fraction inhibited α-glucosidases with IC_{50} values of 700 and 250 μg/mL, lipase with 480 and 718 μg/mL, whereas *C. sinensis* displayed enzymatic inhibition at IC_{50} values of 260 and 587 μg/mL, respectively. Gallic acid, ethyl gallate showed the highest and competitive inhibition of α-glucosidases (IC_{50} 832 μM and 969 μM, respectively), while isoorientin was the most active compound in the uncompetitive lipase inhibitors (IC_{50} 201 μM) (Morales *et al.,* 2018). Lin et al. published a study on *L. octovalvis* extract (LOE) in differentiated C2C12 muscle cells, HepG2 hepatocellular cells, STZ-induced diabetic mice and HFD-induced diabetic mice, which reported an obvious reduction in the hyperglycemia of this extract. LOE and its bioactive compound (β-sitosterol) stimulated significantly the phosphorylation of AMPK in C2C12 muscle and HepG2 hepatocellular cells. In STZ-induced diabetic mice, both LOE and β-sitosterol showed an anti-hyperglycemic potential when compared to metformin, an antidiabetic standard drug. Furthermore, mice fed a HFD enhanced glycemic control and memory presentation after the treatment of LOE (Lin *et al.,* 2017).

Andrographis paniculata Nees

Andrographis paniculata known as a valuable natural product is widely used in traditional medicine for improvement of hepatic and cardiovascular function as well as treatment of diarrhea, fever, respiratory illness and as an antioxidant. The phytochemicals of *A. paniculata* revealed that it may contain over 55 ent-labdane diterpenoids, 30 flavonoids, 8 quinic acids, 5 rare noriridoids and 4 xanthones (Hossain *et al.,* 2014). Andrographolide is the major active component derived from this medicinal herb. An *in vivo* study showed the improvement of Andrographolide on streptozotocin (STZ)-induced diabetic retinopathy in mice. The results suggested that this compound prevented the expansion of retinal vessels in STZ-induced proliferative diabetic retinopathy mice, which was exhibited by immunofluorescence staining for cluster of differentiation. In STZ-induced non-proliferative diabetic retinopathy mice, Evans blue permeation results showed the reduction in blood-retinal barrier malfunction by the treatment of Andrographolide. Moreover, Andrographolide also reduced the increase in vascular endothelial growth factor (VEGF) and vitreous cavity, retinal mRNA expression of VEGF and serpine1, IL-1β, IL-6, TNF-α and tissue factors (Yu *et al.,* 2015). Li has synthesized a new andrographolide derivative AL-1 by the conjugation of andrographolide and lipoic acid, then indicated the influence of AL-1 on insulin resistance in a high-fat diet/streptozocin-induced diabetic rats as well as unclear mechanism related to its action (Li *et al.,* 2015). These results showed a significant hypoglycaemic potential of AL-1 (40 and 80 mg/kg). It also increased HDL level and insulin sensitivity, concurrently, reduced cholesterol level and the homeostasis model assessment of insulin resistance. Furthermore, AL-1 restored mass and function of pancreatic tissues, inhibited phosphorylation of p65 and IκBα in RIN-m cells caused by high glucose state (Li *et al.,* 2015). Deoxyandrographolide (DeoAn), another bioactive constituent extracted from the *A. paniculata* also exhibited the effects on use of glucose for muscle movement and blood glucose levels. A dose-dependent administration of this compound had the ability to ameliorate glucose transporter 4 (GLUT4) translocation, leading to glucose uptake with no change in the total content of GLUT4 and GLUT1 in L6 myotubes. It also stimulated PI-3-K- and AMPK-dependent signaling pathways followed by increasing in glucose transportation. Additionally, STZ-induced diabetic rats treated with DeoAn

exhibited lower postprandial blood glucose levels concurrently, the repression of increase in seum insulin, FSG, triglycerides and LDL- cholesterols was found in db/db mice (Arha *et al.,* 2015). Akhtar et al. indicated that *A. paniculata* plant extract also had anti-diabetic capacity for obese and obese mice models. When compared with normal groups, the amount of allantoin, creatinine and lactate increased significantly in the urine of obese groups, while the high concentrations of glucose, taurine and choline as well as the decrease of lactate, acetate, formate, succinate, acetoacetate, citrate, 2-oxoglutarate, dimethylamine, creatinine, hippurate and allantoin levels were observed in obese-diabetic rats. *A. paniculata* leaf aqueous extract improved the disturbed metabolic functions of obese-diabetic rats close to physiological conditions (Akhtar *et al.,* 2016). Of note, treatment with *A. paniculata* leaf extract (50, 100 and 200 mg/kg/day), or with pure Andro (15, 30 and 60 mg/kg/day) also reduced cognitive decline and oxidative stress, induced acetylcholinesterase inhibition, ameliorated hyperglycemic state and lack of insulin in diabetic rats (Thakur *et al.,* 2016).

Trigonella foenum-graecum L.

Trigonella foenum-graecum (Methika in Sanskrit) has been used in India folk medicine as a kaphahara (balancing kapha) herb for indicating in Prameha or early diabetes mellitus and reducing lipid levels of blood. The LC–MS/MS analyses showed various bioactive compounds isolated from *Trigonella* like apigenin, quercetin, kaempferol, calycosin, pratensin, orientin, tricin, luteolin and gallic acid (Banerjee *et al.,* 2019). In a streptozotocin-induced diabetic rat model, *Trigonella foenum-graecum* remarkablely decreased the FSG back towards normal levels. It showed antioxidant property to defend the organs like liver and pancreas by reducing of TBARS levels and enhancing antioxidant activities (Sankar *et al.,* 2012). According to another study, *Trigonella foenum-graecum* also displayed anti-hyperglycemic effect and ameliorated the levels of hydrogen peroxide, malondialdehyde and 4-hydroxynonanal, the activities of catalase, superoxide dismutase and glutathione peroxidase as well as transcription of thgenes of these enzymes in liver and brain tissues of diabetic mice (Sharma *et al.,* 2015). In a clinical trial, *T. foenum-graecum* seed powder solution showed several therapeutic benefit on lipid metabolism in newly diagnosed T2D patients, including decreased levels of triglycerides, total cholesterol and LDL- cholesterol, concurrently, increased HDL-cholesterol level. Hence, *T. foenum-graecum* may contribute new effective alternatives for the symptomatic improvement in T2D patients (Geberemeskel *et al.,* 2019).

Tinospora cordifolia

Tinospora cordifolia has been widely used as an herbal source for the treatment of several human ailments, including diabetes mellitus (Rajalakshmi & Anita, 2016). The chemical components of *Tinospora cordifolia* included different groups such as phenolics, alkaloids, steroids, glycosides, polysaccharides, aliphatic compounds and the higher levels of protein, phosphorus and calcium were found in leaves. Spectroscopic studies established the structure of clerodane furono diterpene glucoside (amritoside A, B, C, and D) in stem (P. Sharma *et al.,* 2019). Both *in vitro* and *in vivo* analysis showed that sedimental extract of *Tinospora cordifolia* presented antioxidant capacity of around 2046 times and as a potential drug to ameliorate many signals of tissue damages in chronic diseases like diabetes (Kannadhasan & Venkataraman, 2013). Agrawal et al. investigated the therapeutic potential of *Tinospora cordifolia* in diabetic retinopathy in STZ-induced rats, particularly its antihyperglycemic, angiogenic, antioxidant and anti-inflammatory properties. The results indicated decrease in blood glucose and glycated hemoglobin

in mice for 24 weeks after use of *Tinospora cordifolia* extract (250 mg/kg). It also prevented cataract development, reduction of glutathione and catalase and thickening of basement membrane of the retinal and glomerular vasculature of diabetic rat. Treatment with *Tinospora cordifolia* decreased destruction of pancreatic islet structure, angiogenic markers and anti-inflammatory factors TNF-α and IL-1β, which are different biomarkers of diabetic retinopathy (Agrawal *et al.,* 2012). Furthermore, the hydrophilic extract of *Tinospora cordifolia* stem (TCSE) increased insulin secretion and cell viability in rat insulinoma (RIN)-m5F cells as well as the glucose uptake and GLUT4 translocation in 3 T3-L1 adipocytes via PI3K pathway. Rats administered TCSE presented reduction of total cholesterol, triglyceride, dipeptidyl peptidase-4, and TBARS, concurrently, increase in hepatic glycogen and insulin levels as well as glucose transporter 4 protein expression in adipose tissue and liver (Sharma *et al.,* 2019). Another study reported that a novel polysaccharide extracted from *Tinospora cordifolia* methanolic extract significantly reduced plasma glucose, HbA1c, total cholesterol, triglycerides, and increased HDL cholesterol, hemoglobin and tissue glycogen. In addition, this compound had the ability to restore insulin, the altered enzymes associated with carbohydrate metabolism, C-peptide, (14) C-glucose oxidation levels and regenerate β-cells in pancreatic islets (Rajalakshmi & Anita, 2016).

Fagonia cretica

The active compounds isolated from a crude extract of *Fagonia cretica* included stigmasterol, quinovic acid, quinovic acid-3β-O-β-D-glucopyranosyl-(28®1)-β-D-glucopyranosyl ester and quinovic acid-3β-O-β-D-glycopyranoside, both of them presented effects on DDP-4 inhibition with IC_{50} values of 30.7, 57.9, 23.5 and >100 μM, respectively (Saleem *et al.,* 2014). The presence of some phenolic glycosides, such as quercetin-3-O-rutinoside, kaempferol-3(6'-malonylglucoside, kaempferol-3-O-glycoside, kaempferol-3-O-rutinoside, isorhamnetin-3-O-rutinoside, and isorhamnetin 3-(6''-malonylglucoside) in *Fagonia cretica* were reported. Nazir et al showed the α-glucosidase inhibition of *Fagonia cretica*, leading to decrease plasma glucose level and the prevention pancreatic islet cells from damages caused by streptozotocin or nictotinamide treatment (Nazir *et al.,* 2017). Furthermore, *Fagonia cretica* extracts also induced production of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1, enhanced cellular hormone content, and upregulated gene expression of GIP, prohormone convertase and proglucagon (Jafri *et al.,* 2016).

Ficus bengalensis

Traditional medicines have considered *Ficus bengalensis* as benefical, economical and safe ethnomedicines for several human ailments. The therapeutic potential of *Ficus bengalensis* roots and barks was reported for the treatment of T2D due to decrease in FSG level in diabetic rats (Singh *et al.,* 2009). In an animal hypercholesterolaemic model, rabbits treated with *Ficus bengalensis* aqueous bark extract showed the low levels of triacylglycerol, cholesterol, LDL, VLDL-cholesterol and reduction of lipid peroxidation. This extract also activated various antioxidant enzymes including catalase, superoxide dismutase, glutathione reductase and glutathione peroxidase (Shukla *et al.,* 2004). Moreover, *Ficus bengalensis* had the ability to restore amount of serum glycolytic, electrolytes enzymes and hepatic cytochrome P450 dependent enzyme systems and decrease the production of liver and kidney lipid peroxides in diabetic rats. However, detailed studies are established to further investigate the therapeutic effects of *Ficus bengalensis* on diabetes mellitus (Gayathri & Kannabiran, 2008).

CONCLUSION

In conclusion, biological active compounds of plants and natural extracts acting through different mechanisms are effective therapeutic alternatives for the prevention of T2D development. Since studies with several of these medicinal plants are explorative and desultory, it is necessary to investigate comprehensively and find new potential candidates for future use.

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Chapter 10
Efficacy of Phytochemicals and Natural Products in the Management/Treatment of Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative illnesses are disorders that cause considerable loss of neurons, both structurally and functionally, and affect millions of people globally. These disorders include Parkinson's disease, which is characterized by the loss of dopaminergic nigrostriatal neurons; Huntington's disease, characterized by the loss of spiny, medium-sized striatal neurons; and Alzheimer's disease (AD), characterized by cerebral atrophy. As a result of current therapeutic procedures and the progressive nature of these diseases, a number of side effects have emerged, prompting patients to seek alternative treatment. The concept of neuroprotection concerns the administration of a specific agent, which should reverse some of the damage or prevent further adverse changes associated with these disorders. The involvement of medicinal plants and natural products in such situations has proven advantageous due to their manifestation through many cellular and molecular pathways. This chapter focuses on role of phytochemicals and natural products on major pathological factors in NDs.

INTRODUCTION

Neurodegenerative diseases (NDs) are devastating diseases which adversely altered motor or cognos-

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cible responsibilities and are swiftly emerging a worldwide disease having about 47 million individuals globally suffering derangement. These diseases are characterized by gradual dysfunction in nerve cells and neuronal loss. Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) are notable types of neurodegenerative diseases (Matilla-Duenas *et al.,* 2014; Oladele *et al*., 2021a). NDs represent significant health risks, particularly in the elderly population (Hamer & Chida, 2009). For example, Parkinson's disease is the second most common neurodegenerative disease, negatively impacting 1 to 2% of the persons over the age of 65, while Alzheimer's disease is the 6th major cause of mortality in the United States (Bekris *et al.,* 2010; Alzheimer's Association, 2016).

Alzheimer's disease (AD) is the most common cause of dementia (Alzheimer's Association, 2016), which is defined by a decline in cognitive function, notably memory, and the inability to carry out daily tasks (Alzheimer's Association, 2016). The aggregation of neurofibrillary tau tangles (NFTs) and amyloid beta (Aβ) plaques in the nerve cells which disturb neuronal functional impulses has been recognized as key in the aetiology of AD. Tau proteins are regulated and enhanced via phosphorylation by phosphatases and glycogen synthase kinase 3β (GSK-3B) to carry out its biological functions (Mi & Johnson, 2006). Many disorders of the lysosomal system are implicated to ensue owing to dysregulation in the degradation of tau protein due to multiple phosphorylations, ultimately resulting in the development of extracellular NFTs which cause a disturbance on the neural network and degenerate to a pathological state known as Alzheimer's disease (Murphy & Lii, 2010).

Parkinson's disease (PD) is the second most prevalent ND, with two types: sporadic PD (which accounts for more than 90% of cases) and familial PD (which accounts for the remaining 10% of cases), with over twenty genes linked with this disease (Deng *et al.,* 2017). Autosomal dominant is caused by aberrations in α-syn or LRRK2 (leucine-rich repeat kinase 2) while mutation in UCHL1 (ubiquitin C-terminal hydrolase 1), Parkin, DJ-1 or PINK1 (PTEN induced putative kinase 1) has been reported to cause autosomal recessive (Yao *et al.,* 2010; Helferich *et al.,* 2016). Moreover, chromosome 2 and X have been associated with Parkinson's vulnerability. The α-Syn is an important protein that plays a critical role in the molecular pathogenesis of PD in both familial and sporadic forms of the disease (Winslow *et al.,* 2010). The complicated pathophysiology of neurodegenerative diseases has not been fully understood; nevertheless, existing data from research and clinical trials demonstrated these diseases are typified by neuroinflammation, oxidative stress, cell death as well as protein misfolding. As high levels of oxidative stress are commonly documented in the brain areas of individuals suffering from various types of neurodegenerations, reactive oxygen species (ROS) may play an important role in disease etiology (Dias *et al.,* 2013; Oladele *et al.,* 2021a).

ROS are chemically reactive molecules that are spontaneously produced within the biological system and play important roles in modulating cellular processes such as stressor responses, cell survival, and inflammation. Nevertheless, if their levels are not effectively controlled or managed, they can be harmful to health and contribute to the pathogenesis of a variety of illnesses, including neurological diseases, cancer, allergies, muscle dysfunction, and cardiovascular problems (Zuo *et al.,* 2013; He & Zuo, 2015; Oladele *et al*., 2021c; 2021d). Because of their reactivity, the presence of large concentration of these reactive species may induce oxidative stress (OS), which is characterized by disruption in the equilibrium between antioxidant and pro-oxidants in bio-systems, coupled with mitotic catastrophe if unmanaged (Zuo *et al.,* 2015).

A variety of preclinical experiments have been conducted to determine the role of oxidative stress in neurodegenerative disorders (St-Pierre *et al.,* 2006; Hensley *et al.,* 2006; Oladele *et al*., 2020a). ROS may not be able to cause neurodegenerative diseases on their own, but they can exacerbate disease pro-

gression by causing damage to key macromolecules and altering mitochondrial functions (Dias *et al*., 2013). Remarkably, neurons are prone to oxidative damage due to significant polyunsaturated fatty acid membrane content, ineffective antioxidant defense, and high oxygen consumption (Rego & Oliveira, 2003). Endogenous antioxidants maintain free radicals and reactive oxygen species generated by NADPH oxidase (Nox), xanthine oxidase (XO), mitochondria, and at moderately low levels under resting conditions (Zuo *et al.,* 2015). However, aberrations in the mitochondria functions and/or inflammation of the neurons can modify and disrupt the redox balance (Rego & Oliveira, 2003).

Several indications from cellular, genetic, neuropathological and biochemical investigations have demonstrated that monomeric proteins can misfold, oligomerized, form aggregates and become accumulated in the brain, which is the major cascade of processes that activate pathological abnormalities associated with neurodegenerative diseases (Goedert, 2015). The following proteins in neurodegenerative diseases have reported to involve cerebral misfolded aggregates accumulation: prion proteins in chronic wasting disease, prion diseases (PrDs) (i.e., Creutzfeldt–Jakob disease (CJD), scrapie, and bovine spongiform encephalopathy; and TAR DNA-binding protein 43 (TDP-43) in frontotemporal dementia and amyotrophic lateral sclerosis; dementia with Lewy bodies and multiple system atrophy, alpha-synuclein (α -Syn) in PD; amyloid-beta (Aβ) in AD; tau in chronic traumatic encephalopathy, frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, argyrophilic grain disease, and AD. Although the formation of protein aggregates differs amongst neurodegenerative illnesses, their pathogenic processes are clearly alike (Soto, 2003). The prophylactic use of natural products and plant derived bioactive agents in the treatment and management of diseases such as neurodegenerative diseases, cardiovascular diseases, and cancer have continuously been discovered (Oladele *et al*., 2017, 2019, 2020a). Plants are sources of therapeutic chemicals and have played a significant role in human health maintenance over time. Natural products account for more than half of all current clinical medications, and they play an essential part novel drug development strategy. The protective potential of phytochemicals in the neuronal system have been documented (Oladele *et al.,* 2017, 2019, 2020b 2020c). As a result, there is a rising interest in developing pharmaceutical and nutritional treatments to prevent oxidative stress-induced damage to the central nervous system, with dietary antioxidants, natural products, and phytochemicals being studied for their possible neuroprotective properties.

In this context, this chapter present a review on the pathogenesis of selected neurodegenerative diseases focusing oxidative stress, neuroinflammation, apoptosis and protein misfolding and aggregation as major pathological factors in neurodegenerative diseases. The role of phytochemicals and natural products on these major pathological indices was also discussed.

PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Inflammation in Pathogenesis of Neurodegenerative Diseases

Inflammation is part of the body's complex physiological response to harmful stimuli or assault induced by intrinsic or extrinsic causes. This defensive strategy, however, might be harmful if it is not well coordinated/ deployed. In NDs, inflammation can be caused by misfolded protein aggregation, the build-up of improperly changed cellular components, the reaction to chemicals released after neuronal injury, and incorrect modulation of inflammatory regulatory mechanisms (Wyss-Coray & Mucke, 2002). Microglia are tightly connected with neurons producing Aβ in Alzheimer's disease. Aβ deposits in the brain, on the

other hand, are believed to be connected with an inflammatory response that results in elevated levels of vital defense proteins and transcription factors (Akiyama et *al., 2*000).

Microglial cells communicate with one another via a family of receptors known as pattern recognition receptors (PRRs) which includes Toll-like receptors (TLRs). TLRs connect with invar molecular motifs confirmed by infectious pathogens' pathogen associated molecular patterns (PAMPs) or endogenous danger-associated molecular patterns (DAMPs) released by injured tissues. Aβ, α-synuclein, and microtubule-associated protein tau are among the DAMPs that have been found. Microglia and astrocytes can express a variety of TLRs, which when activated can increase the secretion of proinflammatory cytokines such as TNF-α and IL-6, as well as chemokines such as IL-8 (Bsibsi et a*l., 200*2; Amor et a*l., 201*0).

Increased proinflammatory cytokines levels are frequent in the cerebrospinal fluid, blood, and post-mortem brain tissue of PD patients, as they are in AD (Akama & Van Eldik, 2000; Swardfager et *al., 20*10). Following α-synuclein activation, microglia release inflammatory cytokines and activate inflammation-mediating enzymes such as matrix metalloproteinases (MMPs) (Lee et a*l., 201*0; Glass et a*l., 201*0). A component of leucine-rich repeat family, pyrin domain containing 3 (NLRP3), and inflammasomes, nucleotide-binding domain is expressed by activated microglia. Inflammasomes promote various inflammatory reactions, including the maturation of IL-1 β, which has been showed in animal models to aggravate the course of AD and PD (Singhal et al*., 20*14). As a result, nonsteroidal anti-inflammatory medications have been anticipated to possess beneficial roles (Krause & Muller, 2010).

The protective function of microglia on neurons, cytokines, and other CNS inflammatory and immunological pathways is also well understood (Cappellano et a*l., 201*3). Microglia, for example, play a function in removing apoptotic cells and debris in the CNS. There is additional evidence that microglia enhance fibrillar Aβ removal via micropinocytosis (Takada et al*., 2003*). Chronic stimulation of microglia, on the other hand, may result in the loss of this protective feature, resulting in amplified secretion of various cytokines that suppress phagocytosis and other processes needed for cell survival (Al-Nuaimi et al*., 2012*). Utilizing current information, the revolutionary idea of "neuroinflammation" attempted to clarify the function of inflammation in the cause of Alzheimer's disease coupled with other neurodegenerative diseases. Nevertheless, the debate over beneficial or harmful significance of inflammation to the CNS of neurodegenerative disease patients is still unanswered. Owning to this, "A unified opinion was introduced, indicating that in pathophysiological scenarios, inflammation can play both beneficial and detrimental roles, based on regional conditions and the timeframe of inflammatory processes and shutting-off systems." (Cappellano et al*., 2013*).

Apoptosis in Pathogenesis of Neurodegenerative Diseases

The morphology of apoptosis is defined by the sequence of chromatin condensation, nuclear contents splitting, cell shrinking, and disintegration into minute pieces surrounded by membrane structures. Apoptotic cells are opsonized in vivo by surrounding cells without generating inflammation because the integrity of plasma membranes and cell organelles is conserved and the release of intracellular components is inhibited throughout the suicide program.

Apoptosis may take place locally without having destructive effects on neighbouring healthy cells, as against necrosis, which is characterized by spontaneous cell enlargement and subsequent plasma membrane breakdown. Necrosis frequently causes significant secondary cell rupture in close tissue as a result of the inflammatory response caused by cell rupture. Because necrosis and apoptosis differ biochemically and physically, they were once classed as two distinct types of cell death. There is mounting

evidence that this difference is not really that clear, and that traumatic cell death, at the very least, can be seen as a link between them (Martin, 2001). Apoptosis is a physiological process that provides for the preservation of a constant size and cell number in actively dividing tissues such as the intestinal mucosa, skin, and the immune system, as well as the development of the peripheral and central nervous systems. During synapse development, for example, neuronal death is common (Mattson, 2000). Furthermore, the supply of neurotrophic factors, which promote the survival and proliferation of neurons, appears to be significant for the fate of the particular neuron, due to activation of anti-apoptotic pathways (Mattson & Lindvall, 1997).

Many acute and chronic neurological disorders are characterized by the degeneration of one or more nerve cell types. Many of the prerequisites for apoptotic cell death are met as chronic neurodegenerative diseases advance. As a result, developing new therapeutic options for neurodegenerative illnesses necessitates an insight into the molecular mechanisms underpinning neuronal cell death. Extrinsic and intrinsic apoptosis pathways exist, as do diverse prospective interaction networks between them. The intrinsic pathway is directly related to the quality, integrity, operations and feature of mitochondria within the cell, meanwhile the extrinsic pathway is induced by cell surface mediator of tumour necrosis factor (TNF) family cytokine receptors (Reed, 2000).

Major Mediators of Neuronal Apoptosis

The physiological and chemical alterations associated with apoptosis are propagated by a unique class of subcellular cysteine proteolytic enzymes called *caspases* (cysteine aspartyl-specific proteases), which catalyze their substrates at specific aspartate side chains (Alnemri *et al.,* 1996). Removal of such residues also results in caspase activation. As a result, caspases, coupled with key cellular biomolecules, can self-activate. More or less 14 distinct members of these enzymes have been identified with 11 of them being found in the human genome (Reed, 2002). Based on their amino-terminal properties, they are normally classified as upstream initiator caspases or downstream effector caspases (Reed, 2000). Caspases initiating this cascade may self-interrelate via their elongated inactive-domains; however, function of the short inactive-domain in efferent enzymes have not been fully elucidated. Caspase-8, a protein that initiates the extrinsic signalling pathway, has a death propagating domain at its amino-terminus that it associates with and is activated by similar proteins propagating such activities (12 death effector proteins has been identified). Representative member of these protein family (FADD) also possesses a death domain whose interaction with TNF family death receptors have been well reported (Reed, 2000). Even though the induction of capase-8 in nerve cells by various death signals are documented (Velir *et al*., 1999), the triggering of ensuing programmed cell death by specific ligands and receptors is yet ascertained. Remarkably, the p75 nerve growth factor receptor (p75NGFR) comprises an altered death domain (Liepinsh *et al*., 1997), and its activation can induce apoptosis in neurons under certain conditions (Bredesen *et al*., 1998). Nevertheless, it should be highlighted that developmental and disease-specific activation mechanism may differ greatly, especially since adult neurons no longer exhibit this growth factor (Hu *et al.,* 1998; Hirsch *et al.,* 2000).

There is a lot of facts arising from research in gene deletion and bio-engineered animals that the intrinsic signal transduction system is important for neuronal death. Metabolic stress (hypoxia, hypoglycaemia), development of free radicals (oxidative stress), damage of the plasma membrane components, elevated calcium inflow (excitotoxicity), increased expression of the tumour suppressor gene p53, and DNA damage (hereditary or induced) could result into mitochondrial alterations leading to the develop-

ment of small channels in the membrane of mitochondria and a number of cell death-related chemicals (apoptosis-inducing factor, cytochrome C, SMAC/Diablo) are released.

Bcl-2 family proteins control and moderate changes in mitochondrial function that eventually contribute to cell death. These Bcl-2 family proteins displayed multiplicity (Reed, 2000) in which some are propagate cell death (e.g., Bid, Bax, Bad) while others mitigate or inactivate this process (e.g., Bcl XL, Bcl-2). The development of dimers, as well as the balance shift between pro- and anti-apoptotic Bcl-2 family members, may affect a cell's susceptibility to apoptotic stimuli (Kroemer and Reed, 2000). It has been demonstrated, for example, that calcineurin dephosphorylates Bad in neurons, hence commencing the cell death cascade (Wang *et al*., 1999). Proteins that bind to members of the Bcl-2 family modulate their functions have garnered significant recognition in recent years. The BAG family is one of these Bcl-2 binding proteins with antiapoptotic action (Takayama & Reed, 2001). Through their BAG domain, they all bind to specific molecular chaperone (Hsp70) and link cellular stress responses to the apoptotic death mechanism. BAG1 has been found in neurons as an important protectant of the neurones and key modulator in their development (Kermer *et al.,* 2002). *In vivo,* BAG1 promotes stroke resistance via boosting Hsp70 expression at the posttranscriptional level (Kermer *et al.,* 2003).

The bifunctional apoptosis regulator (BAR) is another Bcl-2 binding protein with neuroprotective effects. BAR is a multidomain protein that was initially found as a Bax-mediated cell death inhibitor (Zhang *et al.,* 2000). It has the ability to block both TNF family death receptor-induced apoptosis and mitochondria-dependent cell death. BAR's association with Bcl-2 or Bcl-XL through a specialized domain may contribute to BAR's apoptotic-quenching capabilities. Furthermore, this protein has a domain similar to traditional death propagating domains (dubbed "pseudo DEDs") which facilitates caspase-8 interaction. As a result, this protein was suggested to function as a linkage protein that connects components of the receptor-induced and mitochondria-dependent apoptotic mechanisms/ pathways. Conclusively, the expression of BAR in the nerve cells is quite pronounced where it enhances thriving of these cells in response to a variety of apoptotic events (Roth *et al.,* 2003).

Cytochrome-c forms oligomeric clusters with Apaf-1 (apoptotic protease activation factor-1) and caspase-9 after being released from mitochondria into the cytoplasm causing the activation of caspase-9 (Zou *et al.,* 1999). Apaf-1 and caspase-9 interact via a CARD domain (caspase-associated recruitment domain) that is found in both proteins (Qin *et al.,* 1999). A mechanism known as 'induced proximity' is thought to be responsible for caspase-9 activation (Salvesen & Dixit, 1999). Several inactive caspase-9 proforms are brought into close proximity to one another by attaching to Apaf-1. Because this caspase's proform has some protease activity, the interaction of numerous caspase molecules promotes cleavage and the transition into the fully active form. Aside from procaspases that contain a CARD domain (caspase-1, -2, -4, -5, and -9), the human genome contains at least 20 CARD proteins that either promote or inhibit apoptosis (Reed, 2000). Active caspase-9 catalyzes the conversion and activates effector caspase-3, which is in charge of driving the cell death program (Hengartner, 2000).

Aside from Bcl-2 and CARD proteins that have apoptosis- propagating or mitigating properties, protein family such as the IAPs (inhibitor of apoptosis proteins) have also been reported with similar functions. These protein family have been extensively identified in bacteria, viruses and humans (Reed, 2000), of which at least one is expressed in neurons (neural apoptosis inhibitory protein). Proteins belonging to this family inhibit 'unplanned' mobilization of effector proteolytic enzymes, however, negatively regulated by the mitochondrial protein Smac/Diablo. As a result, after suitable stimulation, the effective operational sequence of the apoptotic cascade is ensured (Hengartner, 2000). In family

cases of spino-muscular atrophy, inheritable aberrations of neural IAPs are associated with growing neurodegeneration (Roy *et al.,* 1995).

Furthermore, there are additional signalling mechanisms not directly involved with the programmed cell death machinery but are capable of interfering with and inhibiting it. These pathways include the mitogen-activated protein kinase pathway (Fukunaga & Miyamoto, 1998) and the PI3K/Akt signalling pathway (Franke *et al.,* 1997). Other apoptotic-mitigating indicators are propagated by the mobilization of specific transcription factors (Reed, 2000; Bozyczko-Coyne *et al.,* 2002).

PROTEIN MISFOLDING AND AGGREGATION IN NEURODEGENERATIVE DISEASES

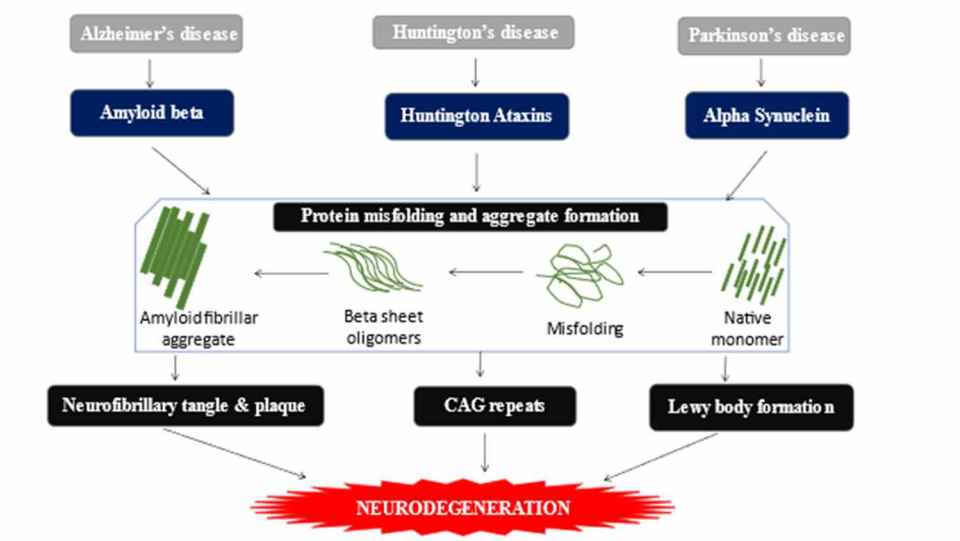
The progressive build-up of misfolded protein aggregates in regular patterns commonly known as amyloid is a pathological feature common to all types of neurodegenerative diseases and it is referred to as the root cause of these diseases (Goedert, 2015). Evidence derived from neuropathological, genetic, cellular, and biochemical investigations have showed that the major events that activate pathological abnormalities associated with neurodegenerative diseases includes cascade of events in which monomeric proteins can misfold, oligomerized, form aggregates and become accumulated in the brain (Goedert, 2015).

These disease-related proteins though do not demonstrate distinct likenesses in terms of expression level, sequence, function, structure, or size. However, these proteins from their native states undergo misfolding to form intermolecular β -sheet-rich structures, ranging from small oligomers to large fibrillar aggregates in the unhealthy brain (Soto, 2003; Goedert, 2015). Amyloid are highly well-organized aggregates, 100–200 Å in diameter, contained arrangements of intermolecular β -sheets running parallel to the long axis of the fibrils, a structure recognized as cross-β (Fitzpatrick *et al.,* 2013). Staining with particular dyes such as thioflavin, Congo red, and related dyes is the most common method for identifying amyloids (Rambaran & Serpell, 2008). Initially, it was thought that these massive protein deposits in the brain were the harmful species; however, evidence from both experimental and clinical studies reveal that smaller, soluble misfolded proteins, precursors of fibrillar aggregates, are the major mediators in ensuing neurodegenerative diseases (Gadad *et al*., 2011).

Misfolded proteins are diverse group of species ranging from dimeric structures to complex protofibrillar structures (Breydo & Uversky, 2015). In their oligomeric conformation, these species are characterized with extreme fluidity in equilibrium relative to their monomeric and fibrillary structures. Furthermore, some of these oligomeric structures are end-products of rogue pathways which could be highly toxic while others are on-pathway intermediates for amyloid fibril formation (Figure 1) (Breydo & Uversky, 2015). The diverse nature, spontaneous species interconversion, and characteristics of forming extremely stable aggregates contributed to the lack of reliable information regarding structural details of misfolded oligomers as well as the structure associated with disease propagation (Breydo & Uversky, 2015).

The mechanism underlying protein misfolding/aggregation can be better defined using the seeding–nucleation model, first proposed by Lansbury and colleagues (Jarrett & Lansbury, 1993), which has been modelled kinetically in great detail (Meisl *et al.,* 2017). During this process, a slow and thermodynamically unfavourable nucleation stage is preceded by a fast elongation phase (Soto *et al.,* 2006). In the nucleation phase, the rate-determining step is the formation of a stable seed or nucleus of polymerized protein. Once the seeds are formed, they rapidly grow by incorporating monomeric protein into the polymer (Soto *et al.,* 2006). Bulky polymeric aggregates can break in a procedure not yet fully

Figure 1. Mechanism of Protein Misfolding and Aggregate Formation in Neurodegenerative diseases



elucidated internally to produce more nuclei to continue the process. A distinctive characteristic of the seeding–nucleation model is the capability of preformed seeds to significantly enhance the aggregation process by engaging the soluble normal protein into the growing aggregate (Soto *et al.,* 2006). Using biophysical mode of analysis, the procedure by which protein misfold and aggregates includes the rearrangement of the protein structures into a series of highly stabilized β -strands. These structures possess open up 'sticky' ends for attracting folded or partially unfolded proteins, forcing its misfolding to fit into the cross-β polymeric structure. Although the primary scaffold of the misfolded aggregates is similar, the individual molecules can adopt many quite varied structures, which give rise to the possibility of conformational strains.

Even with the unities in the disease mechanisms of neurodegenerative disorders, vital significant differences exist between the key diseases: genes implicated, cellular types injured, areas of the brain affected, clinical symptoms, risk factors, and prevalence. Furthermore, the pathogenesis of each of the well-studied neurodegenerative disease is linked with the misfolding and aggregation of a specific protein that forms deposits that accumulate in diverse cellular locations. Conclusively, although there are immense structural similarities among these protein aggregates, their individual structures are likely to be a distinguishing factor depending on the affected protein and ensuing disease, which most likely contribute to their mechanism of cellular toxicities.

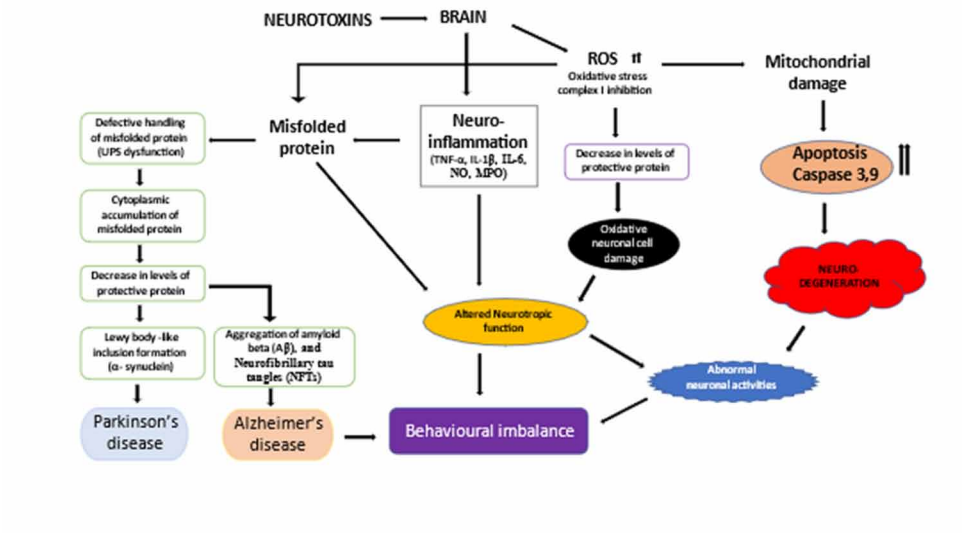
OXIDATIVE STRESS IN PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Oxidative Stress in Pathogenesis of Parkinson's Disease (PD)

Parkinson's disease is the second major neurodegenerative diseases, characterized by the disintegration of dopaminergic nerve cells in the brain (McCormack *et al.,* 2002). About 1-2 percent of the total population of persons above the age of 65 suffer Parkinson's disease, and the occurrence increases to

4% in individuals over the age of 85 (Farrer, 2006; Oladele *et al*., 2020a). The pathological mechanism underlying dopaminergic neuron degeneration has been linked to an excess of reactive oxygen/nitrogen species and other free radicals. Excessive ROS production can be caused by either mitochondrial dysfunction or inflammation (Dias *et al.,* 2013). Redox homeostasis is required for the biological functions of redox-sensitive signaling proteins in brain cells and neuronal survival (Chinta & Anderson, 2008). The nerve cell and glia mitochondria are the primary source of reactive oxygen/nitrogen species in the brain (Figure 23.2). (Dias *et al.,* 2013). The production of ROS is increased in Parkinson's disease due to high levels of iron or Ca^{2+}, GSH depletion, aging, mitochondrial dysfunction, dopamine degradation, and neuroinflammation (Dias *et al.,* 2013).

Figure 2. Molecular Pathogenesis of Neurodegenerative Diseases



Therefore, when individuals suffering Parkinson's disease have contact with triggering factors or chemicals including dopamine, neurotoxins, and pesticides, ROS secretion may be aggravated (Gangemi *et al.,* 2016). This confirmed that there is a connection between chemicals exposure and Parkinson's disease (Gangemi *et al.,* 2016). ROS have been implicated in the loss of dopaminergic neurons (Dias *et al.,* 2013). Several research findings suggest that the presence of neuromelanin is connected to distinguishing damage associated with dopaminergic neurons, because neurons showing high pigmentation are even more susceptible to damage (Perfeito *et al.,* 2012). The formation of neuromelanin appears to be linked to dopamine auto-oxidation, a ROS-mediated pathway that takes precedence over secretion (Perfeito *et al.,* 2012).

ROS are produced during neurodegeneration, which can damage vital cellular proteins and alter membrane integrity, causing oxidative stress. Dysfunction of the mitochondria raises the level of free radicals in the respiratory chain (Dias *et al.,* 2013). There exists established connection between PD and mitochondrial complex I deficiencies in particular (Zuo & Motherwell, 2013). This impairment is linked to a mutation in the PTEN-induced putative kinase 1 gene (PINK1), an enzyme ubiquitous in human and function in reducing oxidative stress (Zuo & Motherwell, 2013). The PINK1 mutation has been connected

to the development of Parkinson's disease (Zuo & Motherwell, 2013). Mutations in leucine-rich repeat kinase 2 (LRRK2), parkin, alpha-synuclein (α-syn), and DJ-1 have been related to PD development. These genetic alterations may affect function of the mitochondria, increasing reactive oxygen species (ROS) generation and sensitivity to oxidative stress. Because of its participation in decreasing reactive species and regulating the generation of nerve cell-toxic proteins generated by targeted degradation, mutant parkin may participate in important roles in the occurrence of autosomal recessive Parkinson's disease (Zuo & Motherwell, 2013). Furthermore, α-syn accumulation affect mitochondrial complex I functions, resulting in decreased energy generation and mitochondrial malfunction. Malfunction of the proteasome system, mostly aggravated by dopamine-associated reactive species, is also a contributing factor in PD onset (Ganguly *et al.,* 2017).

Role of Oxidative Stress in Pathogenesis of Alzheimer's Disease (AD)

Of all known NDs, Alzheimer's disease (AD) is quite common, characterized with progressive decreases in behaviour, memory, and functioning that severely impair daily activities (Zuo *et al.*, 2015). AD pathogenesis is principally connected to the production of amyloid beta (Aβ) and extracellular intracellular tau neurofibrillary tangles (NFT) (Figure 23.2) (Butterfield, 2014). Endoplasmic reticulum (ER) plaques can limit Ca^{2+} storage, causing Ca^{2+} overproduction in the cytosol. Similarly, an increase in Ca^{2+} concentration in the cytosol depletes the level of antioxidant enzymes, and reactive oxygen species accumulates within the cells (Ferreiro *et al.,* 2008). ROS-induced ROS over-secretion also leads to Aβ accumulation and production in AD, causing oxidative stress to emerge as a major component in the AD occurrence (Bonda *et al.,* 2010). Malfunction of the mitochondria can lead to increased ROS generation, reduced ATP synthesis, altered Ca^{2+} homeostasis, and excitotoxicity. All of these changes might have a role in the development of Alzheimer's disease (Huang *et al.,* 2016).

Oversensitization of N-methyl-D-aspartate-type glutamate receptors (NMDARs) in Alzheimer's patients can result in severe oxidative damage. This receptor sensitization has been shown to cause severe Ca^{2+} invasion by increasing cell permeability and producing neurotoxic amounts of reactive oxygen and nitrogen species (RNS) (Nakamura & Lipton, 2010; 2011). Reactive oxygen species can mediate JNK/stress-activated protein kinase pathways (ROS). Both tau protein hyperphosphorylation and Aβ-mediated apoptosis have been connected to the activation of these cascades (Patten *et al.,* 2010). Additionally, by activating NADPH oxidase, Aβ proteins can instantly mediate the generation of free radicals (Shelat *et al.,* 2008). The stimulation of p38 mitogen activated protein kinase (p38 MAPK) by Aβ-mediated ROS overproduction changes cellular signalling pathways and causes tau over phosphorylation. The creation of intracellular NFTs may be induced by an uneven aggregation of over phosphorylated tau proteins (Bulat & Widmann, 2009; Giraldo *et al.,* 2014). As a result, Aβ has been shown to play an important role in the triggering of cellular apoptosis (Agostinho *et al.,* 2008). Aβ may increase calcineurin activity, which subsequently stimulates the Bcl-2-associated death promoter, resulting in mitochondrial cytochrome c release (Awasthi *et al.,* 2005). Aβ may also interact with caspases directly, resulting in neuron apoptosis (Awasthi *et al.,* 2005).

Certain dietary variables (for example, redox-active metals), inflammation, aging, and environmental stress can all cause a rise in Aβ production by producing extra oxidative stress (Smith *et al.,* 2010; Hamilton & Holscher, 2012). The aged persons are more prone to oxidative stress, illuminating their susceptibility to this disease (Hamilton & Holscher, 2012). Inflammation causes elevated amounts of cytokines, ROS, and cellular damage, all of which hasten AD emergence (Holmes *et al.,* 2009). Fol-

lowing Aβ deposition, microglia become activated (Seabrook *et al.,* 2006). It is becoming clear that sustained stimulation of microglia results in the secretion of pro-inflammatory cytokines, stimulating a pro-inflammatory event and causing neuronal loss and damage (Wang *et al.,* 2015). Toxins, radiation, and chemicals in the environment can all contribute to oxidative stress (Nizzari *et al.,* 2012). Where there is an abundance of iron, the production of reactive oxygen species (ROS) increases (Nizzari *et al.,* 2012). Because A may directly react with metal ions to form free radicals, methionine 35 plays an essential part in this chain reaction (Nizzari *et al.,* 2012; Butterfield & Boyd-Kimball, 2005). Structural evidence relationship between divalent metal-linked Aβ relative to SOD are emerging, suggesting the antioxidant potentials of these complexes (Curtain *et al.,* 2001). Consequently, supplementation of these metals are being proposed as next generation therapeutic strategy in disease pathophysiology (Curtain *et al.,* 2001).

Oxidative Stress in Pathogenesis of Huntington's Disease (HD)

Huntington's Disease, is characterized by the uneven multiplication and repetition of specific nucleotide repeats- cytosine, adenine, and guanine (CAG) in the HTT gene (Labbadia & Morimoto, 2013). This phenomenon consequently leads to an aberration that mediated elongation of the polyglutamine tract, causing an aggregation-prone HTT protein product (Gil-Mohapel *et al.,* 2014). Mutant huntingtin (mHTT) clusters accumulate in the brains of diseased individuals, disrupting transcription and protein quality control, and are implicated in ensuing neurological disorders in HD (Gil-Mohapel *et al.,* 2014). Currently accessible HD therapies are palliative in nature, as they only minimize the impacts of symptoms. No therapy or treatment has completely cured, undo, or stopped the disease development (Labbadia & Morimoto, 2013). Huntingtin mutants have been shown to repress the expression of peroxisome proliferator-activated receptor-coactivator-1 and lower the potency of striatal mitochondrial DNA (Cui *et al.,* 2006; Weydt *et al.,* 2006). Likewise, mutant huntingtin has been identified as an HD mutant that has been associated with the progression of neuronal nuclear inclusion in HD as a consequence of increased cytoplasmic plaque accumulation (Mochel & Haller, 2011). Despite the well-established link between oxidative stress and HD, studies aimed at providing medication for the disease using an antioxidant approach have been unsuccessful (Kumar & Ratan, 2016).

Several studies have reported the connection between oxidative stress and permanent neurone damage (Tunez *et al.,* 2011). In one study to determine the benefits of neuro rehabilitation exercise, the concentrations of well-established indicators of oxidative damage in HD such as neuron-specific enolase (NSE) and 8-hydroxy-2-deoxyguanosine (8-OHdG) were monitored (Ciancarelli *et al.,* 2015). Furthermore, Cu/Zn-SOD (SOD1) has been identified as a potential peripheral index of neuronal oxidative damage, with levels significantly higher in HD patients compared to controls, suggesting a compensatory response to rising oxidative levels in HD patients (Ciancarelli *et al.,* 2015). Nonetheless, the use of SOD1 as an oxidative diagnostic marker in HD is debatable due to conflicting findings that showed varying levels of SOD activity and concentration in HD (Sorolla *et al.,* 2008). After the three-week regimen neurorehabilitation exercise program, there was a marked decline in the levels of 8-OHdG and NSE while SOD1 remained high, indicating that SOD1 may play a neuroprotective role as an antioxidant enzyme mitigating oxidative stress and scavenging free radicals (Ciancarelli *et al.,* 2015). Physical exercise was recommended for HD patients because it may slow disease progression and improve redox homeostasis (Arida *et al.,* 2013).

Research regarding brain energy level in HD are gaining attention in the scientific community. Supporting this premise, elevated lactate concentration coupled with decline in glucose utilization have been

reported in HD patients (Mochel & Haller, 2011). According to scientific analysis, oxidative damage is associated with decreased expression of the glucose transporter (GLUT)-3, which results in lactate accumulation and glucose uptake downregulation (Covarrubias-Pinto *et al.,* 2015). The majority of ATP synthesis occurs through the production of proton motive force via electron transport chain processes (Bonora *et al.,* 2015). mHTT has been shown to play an important role in mitochondrial dysfunction. Panov *et al.* (2002) used electron microscopy to show that the interaction of mitochondrial membranes with the N-terminus of mHTT causes mitochondrial calcium abnormalities. Moreover, mHTT acts by blocking respiratory complex II (Bossy-Wetzel *et al.,* 2008). This change in mitochondrial electron transport could result in an increase in ROS production while decreasing ATP production (Bossy-Wetzel *et al.,* 2008).

BENEFICIAL EFFECTS OF PHYTOCHEMICALS AND NATURAL PRODUCTS IN NEURODEGENERATIVE DISEASES

Phytochemicals in the Treatment and/or Management Neurodegenerative Diseases

There is presently no viable therapy for Parkinson's disease; nevertheless, greater understanding of the function of ROS in disease aetiology (initiation and development) may result in more effective therapies for PD symptoms. Many neuroprotective strategies for reducing mitochondrial oxidative stress in dopaminergic neurons have been developed. Antioxidants have been shown to prevent free radical damage (Mazo *et al.,* 2017; Oladele *et al*., 2019b, 2020c, 2021e, f, g). Ascorbic acid, glutathione, and tocopherol are important antioxidants that can be recycled by the antioxidant lipoic acid. One of the methods through which lipoic acid provided protective benefits against oxidative damage in oxidative stress-induced mitochondrial dysfunction was the secretion of GSH, which increased the decrease of lipid peroxide (Moreire *et al.,* 2010).

In an animal investigation, it was revealed that lipoic acid therapy improved motor coordination and ATP efficiency, contributing to neuroprotection (Zaitone *et al.,* 2012). Furthermore, therapy with lipoic acid in a rotenone rat model of parkinsonian rats resulted in improved motor function and a significant decrease in neuronal lipid peroxide in the brain (Zaitone *et al.,* 2012). Neuroprotective potentials of natural products and phytochemicals such docosahexaenoic acid (DHA), tocopherol, ascorbic acid, polyphenols, *Ginkgo biloba*, and coenzyme Q10 have all been tested in animal trials with impressive results (Oladele *et al.,* 2020). Nevertheless, no clear evidence of their neuroprotective advantages in humans has been discovered (Etminan *et al.,* 2005). These antioxidant drugs could serve as future guidelines for treating Parkinson's disease patients with combination therapy targeted at decreasing ROS generation in the brain and increasing mitochondrial function (Yan *et al.,* 2013). Treatments for Alzheimer's disease are targeted towards reducing the levels of phosphorylated tau, epigenetic modifications, Aβ oligomers, as well as oxidative stress (Dysken *et al.,* 2014). The significant proportion of Alzheimer's disease treatments rely on neuroprotective, anti-inflammatory, and antioxidant compounds (Dumont & Beal, 2011). Therapies that target ROS-induced cascades such as JNK and NF-kB (e.g., resveratrol, tocopherol, and rutin) have shown some promising *in vitro* and *in vivo* results (Zuo *et al.,* 2015). Significant factors such as reaction kinetics and bioavailability (distribution, retention in the targeted region, permeability, and transport) should be considered when using antioxidants (Dumont & Beal, 2011). Numerous ROS-related

neuroprotective therapeutic procedures have shown substantial healing efficacy in Alzheimer's disease treatment. The antioxidant response element (ARE) pathway, which is controlled by nuclear factor erythroid 2-related factor 2 (Nrf2), is a well-known structured response to oxidative stress (Kanninen *et al.,* 2008). When Nrf2 binds to ARE, it triggers the production of some antioxidant genes in a concerted and organized pattern, which can improve oxidative detoxification. Altered Nrf2-ARE pathways were found in the brains of transgenic mice with Alzheimer's disease symptoms, whereas adenoviral Nrf-2 gene transfer improved Nrf2-ARE cascades and validated protective properties against the intoxication of Aβ accumulation (Kanninen *et al.,* 2008). As a consequence, transcriptional modification of endogenous antioxidants may bring tremendous potential to cure Alzheimer's disease symptoms (Kanninen *et al.,* 2008).

Studies have shown that the risk of AD can be reduced with long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) (Szekely *et al*., 2004). This has aroused a great deal of interest in the discovery of new therapies and applications capable of preventing neuroinflammatory-mediated brain injury. New evidence suggests that dietary polyphenols may have neuroprotective effects by suppressing the activation of microglia, which facilitates inflammatory processes in the CNS. Polyphenols have a variety of anti-inflammatory properties which includes: downregulation of proinflammatory transcription factors for instance neuronal signaling pathways including MAPK cascade and NF-κB via their impacts of a number of glial (Spencer *et al*., 2012); Suppression of processes that activatee NADPH oxidase with concomitant ROS secretion in activated glia; repressive action against iNOS induction and subsequent nitric oxide production in response to glial activation; and inhibitory role on the release of cytokines, such as IL-1β and TNF-α, from activated glia. For instance, the flavonol, quercetin has been shown to suppress neuroinflammation by decreasing nitric oxide secretion and expression iNOS gene in microglia (Kao *et al*., 2010) and mitigating inflammatory cytokine secretion, thereby alleviating neuronal damage (Bureau *et al*., 2008). Nevertheless, one of quercetin's key biological metabolites, quercetin-3-sulfate, did not show any anti-inflammatory activity. Notwithstanding, these studies used quercetin concentrations (10–50 M) that were much higher than those found in plasma after ingestion (Manach *et al*., 2005).

Conversely, epicatechin and catechin (10–300 nM) suppressed TNF- release but not iNOS expression or nitric oxide production in primary glial cells (Vafeiadou *et al*., 2009), indicating that flavanols at physiologically relevant concentrations may have the potential to exert anti-inflammatory effects in the central nervous system. Blueberry polyphenols have also been shown to inhibit NO•, IL-1, and TNF- production in activated microglia cells (Lau *et al*., 2007), and the flavanone naringenin has been shown to be extremely effective in reducing LPS/IFN-induced glial cell activation (Vafeiadou *et al*., 2009).

Natural Products in the Treatment and/or Management Neurodegenerative Diseases

Proteins have a variety of roles within the cell and must fold to achieve the proper three-dimensional conformation in order to perform their biological function. Once their purpose has been done, they must be appropriately degraded to avoid any potential damage (Cuanalo-Contreras & Moreno-Gonzalez, 2019). This balance (proteostasis), is a complicated interdependent system that controls several aspects of protein quality control, including synthesis, folding, and destruction. Because proteins play such a crucial part in cellular activity, maintaining the integrity of this system is essential for maintaining functionality and health throughout one's life (Sicari *et al*., 2019). Proteostasis failure has been linked to aging and neurodegenerative diseases. As a result, targeting proteostasis elements seems to be an en-

couraging neuroprotective medicinal method for preventing or slowing the progression of Alzheimer's disease (Cuanalo-Contreras & Moreno-Gonzalez, 2019; Hafycz & Naidoo, 2019).

In this context, natural products derived from plants, animals, bacteria, fungi, and algae have been widely used to cure a variety of diseases since the dawn of human civilization on Earth, given that the bulk of antineoplastic medications is either from natural chemicals or semi-synthetic or synthetic derivatives of natural items (Newman & Cragg, 2016; Mendonça-Junior *et al*., 2021).

Aminosterols: Squalamine and Trodusquemine

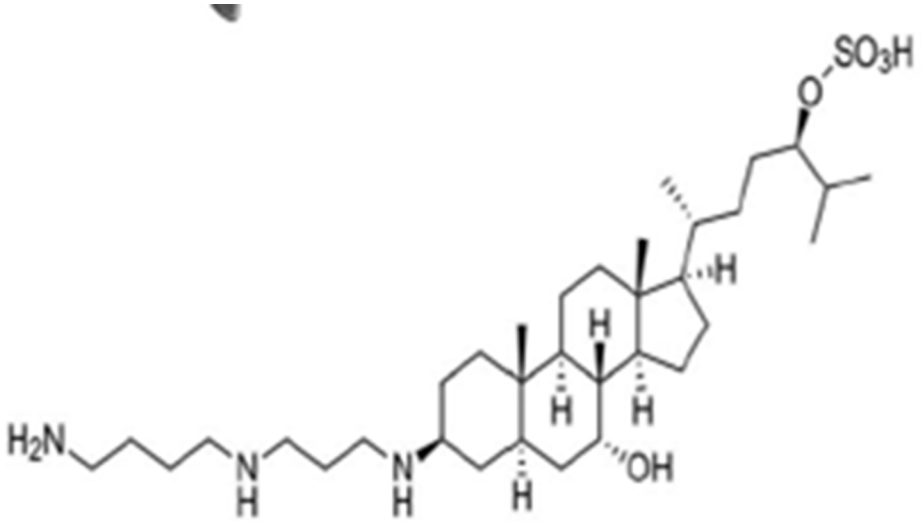
In the 1980s, it was discovered that vertebrates produce antimicrobial peptides, which were later discovered to be an important component of the innate immune system. The finding in 1993 that stomach extracts from *Squalus acanthias* also contained an antibacterial component was the result of a search for antimicrobial chemicals across vertebrate evolution. This molecule was isolated, and analysis of its chemical structure using sophisticated instrumental techniques resulted in the discovery of Squalamine (Figure 23.3) (Moore *et al*., 1993; Limbocker, *et al*., 2022). Squalamine is a highly soluble basic zwitterionic molecule physiological pH (Moore *et al*., 1993). In 2001, during the course of mass-producing squalamine from the dogfish liver, trodusquemine was isolated (Salmi *et al*., 2008). Squalamine and trodusquemine was found to bind more strongly to membranes containing phospholipids with acidic headgroups in aqueous solution and implicated in tackling neurodegenerative diseases by either targeting the mechanism of protein aggregation or aggregates of misfolded proteins (Moore *et al*., 1993; Perni *et al*., 2017). Trodusquemine, unlike squalamine, has been demonstrated to suppress both lipid-induced primary nucleation of a-synuclein and secondary nucleation, a major secondary step in α-synuclein aggregation (Perni *et al*., 2018).

West *et al*. (2020) reported that in Parkinson's disease rat model, squalamine restores the function of the enteric nervous system via interaction with intrinsic primary afferent neurons to restore excitability. Limbocker *et al*. (2021) reported that the suppression of toxicity by these aminosterols and their derivatives is propagated by the removal of harmful oligomers from cellular membranes, providing evidence that these aminosterols could be rationally optimized via drug discovery programs to target oligomer toxicity in specific neurodegenerative diseases.

Honey

Honey is a sweet, viscous liquid made by honeybees *Apis mellifera* from the nectar of flowers and is widely used in apitherapy. Honey's neuroprotective benefits are mediated by inherent phytochemicals, and seen at many neurodegeneration phases (Mijanur Rahman *et al*., 2014). Extensively found in honey, the flavonoid apigenin protects cultured primary hippocampal neurons from oxygen-glucose deprivation/reperfusion-induced damage via increasing sodium/potassium-ATPase (Na+/K+-ATPase) activities, in addition to its radical scavenging activity (Liu *et al*., 2010). Apigenin inhibits CD40 expression caused by interferon-gamma (IFN), which is important for microglia-related immunological responses in the brain. In numerous forms of neurodegenerative illnesses, Rezai-Zadeh *et al*. (2008) proposed that this phytochemical may possess neuro-beneficial and disease-modifying characteristics. Apigenin also promotes adult neurogenesis, which is responsible for learning and memory (Oyefuga *et al*., 2012). Honey pre-treatment remarkably mitigate oxidative stress, neuroinflammation, and programmed cell death in the brain, and the development of nerve cell injury in the piriform cortex of kainic acid-induced rats

Figure 3a. Structure of Squalamine

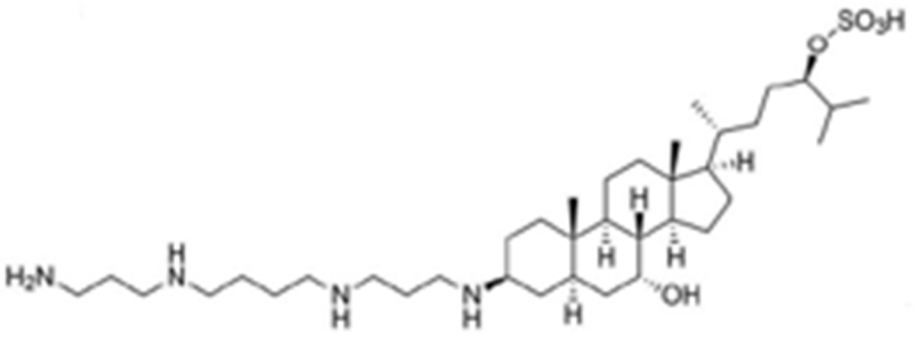


(Mohd Sairazi *et al*., 2018; Hashim & Hatamleh, 2021). Honey has also been shown to alleviate brain oxidative stress and improve hippocampus and medial prefrontal cortex morphological abnormalities in stressed rats (Azman *et al*., 2018).

Bioactive Proteins and Peptides

Peptides produced from innate substances or their synthesized mimics are excellent candidates, according to a growing body of research, among numerous kinds of substances considered neuroprotective agents (Katayama & Nakamura, 2019; Perlikowska, 2021). The diverse actions of peptides open the door to a wide range of applications as medicinal agents or components in therapeutic functional products.

Figure 3b. Structure of Trodusquemine
(Source: Limbocker et al., 2022)



Synthetic peptides can be modified in a variety of ways to achieve desirable properties such as enhanced solubility or intracellular stability, receptor specificity, and better membrane penetration (Perlikowska, 2021). These neuroprotective peptides work directly on the body or act as precursors of physiologically active substances to boost brain health after ingestion. Soybean, walnut, anchovy, and lantern fish have all been reported to possess neuroprotective peptides (Chai *et al*., 2016; Wang *et al*., 2018; Shimzu *et al*., 2018; Zhao *et al*., 2019). Bioactive proteins and peptides, such as those extracted from fish, crustaceans, mollusks, and algae, have also been the subject of much research. These peptides are made up of short amino acids sequence (Ramezanzade *et al*., 2017; Perlikowska, 2021). A peptide's bioactivities are determined by the kind, number, and sequence of amino acids in it, which is more pronounced after proteolytic cleavage or chemical hydrolysis (Najafian & Babji 2012).

The power of certain peptides to ameliorate the symptoms of neurodegenerative disorders has been proven. Peptides from sesame cake (PSC), for example, improved oxidative stress resistance, lowered ROS levels, coupled with reduced amyloid accumulation in a transgenic *Caenorhabditis elegans* model of AD, suggesting that they could help prevent or delay the start of the disease (Ma *et al*., 2017). Mitochondrial failure, generation of ROS, and neuroinflammation are being associated with α-synuclein production in PD (Rocha *et al*., 2018). In a Parkinson's Disease *C. elegans* model, bioactive peptides from sesame seeds reduced α-synuclein aggregation, indicating that this peptide, as a valuable nutraceutical, may prevent and alleviate PD-related diseases (Ma, 2020). According to the findings, PSC reduced not only α-synuclein aggregation, but also MPP+-induced dopaminergic neuron degeneration and food-sensing behavior dysregulation.

Furthermore, peptides have been shown in animal models to reduce tissue inflammation, oxidative stress, and gut dysbiosis, which can help with cognitive decline and hypoxic-ischemic encephalopathy (Ni *et al*., 2019; Wang *et al*., 2019; Zhang *et al*., 2020; Wu *et al*., 2021). In a similar vein, Wu *et al*., (2020) reported two shrimp-derived peptides (QMDDQ and KMDDQ) elicited neuroprotective properties by increasing acetylcholine (ACh) content and inhibiting acetylcholinesterase (AChE) activity. The enhanced neuroprotective effect of QMDDQ could be related to its N-terminal glutamine, which exhibited an expanded spatial structure, facilitating its interactions with AChE, according to the findings.

Zhao *et al*. (2017) investigated the neuroprotective properties of two peptides derived from anchovies hydrolysate with the following structure: Pro-Ala-Tyr-Cys-Ser (PAYCS) and Cys-Val-Gly-Ser-Tyr (CVGST) on glutamate-induced cell death. These compounds decreased ROS and MDA production while increasing the activities of SOD and glutathione peroxidase (GSH-px). Their respective antioxidant activities was thought to be related to Tyrosine and Cysteine residues, as well as their ability to quench free radicals. In LPS-stimulated BV-2 microglial cells, two protein hydrolysates from Cannabis sativa (HPH20A and HPH60A+15AF) reportedly elicited potent anti-neuroinflammatory activities by down-regulating TNF-α, IL-1, and IL-6 mRNA transcriptional levels, in addition to up-regulating gene expression of the anti-inflammatory cytokine IL-10 (Rodriguez-Martin *et al*., 2019). This study's findings imply that *C. sativa* peptide hydrolysates may ameliorate neuroinflammatory and inflammatory states for the first time, bolstering hemp seeds' protein nutraceutical significance.

Marine Bromophenols

Marine bromophenols (MBs), which are mostly extracted from red algae, are said to offer a variety of therapeutic properties. They are usually made up of monomers and dimers of brominated alcohols and alkyl ethers (Fernando *et al.,* 2020). These compounds elicit potent anti-diabetic properties and have

recently been linked to neuroprotection. Paudel *et al*. (2020) identified three bromophenol derivatives from *Symphyocladia latiuscula* and investigated their anti-neurodegenerative disease activity by targeting human monoamine oxidase (hMAO) and G protein-coupled receptors on multiple levels. Their findings showed these compounds interacted with key ligands in the disease propagating mechanism, according to *in silico* analysis. According to these authors, isolated bromophenols are potent inhibitors of hMAO, according to in vitro enzyme inhibition studies. Bromophenol, on the other hand, showed a promising D4R agonist activity with an 18.7l M EC50 value. Inhibition of ChE (cholinesterases), BACE1 (b-site amyloid precursor protein (APP) cleaving enzyme 1), and GSK3b (glycogen synthase kinase-3b) showed that these bromophenols have strong anti-efficacy Alzheimer's (Paudel *et al*. 2019).

CONCLUSION

Currently, pharmacological therapies for neurodegenerative illnesses are centered on increasing nigrostriatal functioning by a continuous supply of dopamine, as well as related procedures to minimize biotransformation and assure dopamine bioavailability in neuronal cells. Nonetheless, these treatments have been relegated to providing only motor-symptomatic relief, obviating their application for non-motor difficulties, particularly during the pre-symptomatic stage. Due to their inability to slow or stop the progression of the disease, these therapies are both curative and preventive ineffective (Kalinderi *et al*., 2011; Style, 2013). Heart problems such as valvulopathy and delusions are associated with the usage of dopamine agonist replacements (Schapira, 1999). Despite the fact that Levodopa (L-dopa), a precursor of dopamine, is associated with severe abnormalities such as dyskinesia when used regularly for more than five years, it has been linked to severe anomalies such as dyskinesia (Jankovic & Stacy, 2007). Furthermore, the safety of numerous peripheral L-Dopa metabolism inhibitors, such as Dopa decarboxylase, monoamine oxidase B, and catechol-O-methyltransferase inhibitors, as well as other techniques, has been questioned due to reported hepatotoxicity and ineffectiveness (Antonini & Poewe, 2007; Kalinderi *et al*., 2011). Meanwhile, other treatments such as deep brain stimulation, neuro-transplantation, and stem cell therapy are intrusive, difficult to get, and costly (Brundin *et al.,* 2010). Neuroprotective agents capable of mitigating, preventing, interfering, and/or reversing the cardinal pathological cascades implicated in extra-nigra and nigrostriatal neuronal death related to neurodegenerative diseases have been proposed as long-term strategies with broad spectrum efficacy against implicated progressive neuronal degeneration (Schapira, 1999; Schapira *et al*., 2006; Chaudhuri & Schapira, 2009). These proposed neuroprotective medicines should be able to protect mitochondria from both internal and external attacks, ameliorate oxidative stress/damage, disperse free radicals, reduce inflammation, and/or inhibit apoptosis as mechanisms of action (Style, 2013; Chao *et al*., 2014). Given the importance of apoptosis, neuroinflammation, protein misfolding, and oxidative stress in neurodegenerative diseases, manipulating important mediators in each of the pathological mechanisms could be a promising intervention option for halting, retarding, or slowing neurodegeneration and alleviating associated symptoms. Antioxidant, anti-inflammatory, antiapoptotic, and neurotrophic pathways were discovered in preclinical trials as underpinning the apparent neuroprotective effects of medicinal plants (Oladele *et al*., 2021b). The discovery and development of novel neuroprotective medicines for neurodegenerative illnesses will be aided by a better understanding of these pathways at the molecular level.

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Chapter 11
Phytochemicals as Antimicrobial Agents: Applications in Infectious Diseases

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ABSTRACT

Microbial infections and antibiotic resistance are two of the most serious threats to society's health today. Millions of people die each year as a result of microbial infections. In 2020, the COVID-19 pandemic caused by viral infections was responsible for the highest amount of all deaths that year. Existing antimicrobial drugs have become less effective, if not ineffective, as a result of the emergence of resistance. Several antibiotic resistance-fighting strategies have been proposed in recent years. One strategy proposed to achieve this objective has been to use combination therapy which appears to restore the desired antimicrobial activity. Several medicinal plants have demonstrated therapeutic effects against pathogens that cause human infections due to their phytochemicals constituents which have been elucidated to act as antimicrobial agents. This chapter focuses on phytochemicals as antimicrobial agents, giving information about infectious diseases and the pathobiology of these diseases. Also, the mechanisms of antimicrobial activity of phytochemical were discussed.

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INTRODUCTION

Over the last million years, human population growth has been adversely affected by the emergence of highly contagious and virulent diseases (McMichae, 2004), which has had a global impact on the environment. Agriculture contributed to this as well, because these highly contagious diseases could only be continuous in huge and densely populated regions (Wolfe *et al.,* 2007). Discovery of antibiotics coupled with substantialdevelopments in antimicrobial therapeutics has enhanced human wellbeing and health by improving infection management and/or treatment (Aminov, 2010). However, prolonged antibiotic use resulted in bacterial adaptation and could also lead to multidrug resistance (Tenover, 2006). Antibiotic efficacy has been significantly reduced due to multidrug resistance, as a result, necessitating a quest for substitute antimicrobial treatment strategies.

Most infections and illnesses are caused by the pertinaciousness of bacteria in alocation and their interaction with humans. Bacterial infections are facilitated by a variety of virulence factors that facilitate various aspects of their pathophysiology that are critical for disease in the host (Falkow, 1991). Membrane proteins and adhesins, for example, facilitate bacterial colonization, attachment, and invasion of host cells. Furthermore, microbial toxins cause tissue damage in the host, and bacterial cell wall machineriessuch as capsular polysaccharides impart resistance to the host immune system (Taylor & Roberts, 2005). Spore formation and biofilm developing ability are two further virulence features that aid pathogen persistence in severe environmental circumstances.

Medicinal plants have performed important functions in the well-being and development of human evolution since ancient times. To maintain human health and prevent food spoilage, a variety of plant products including spices have been utilized as dietary supplements, flavor enhancers, and food preservatives. Furthermore, products of plant origin have been widely utilized in herbal and traditional medicine for disease control, both prophylactically and therapeutically. Several plant-derived compounds have been shown to have antimicrobial activity (Burt, 2004), and a diverse range of active components have been identified (Dixon, 2001). The majority of these compounds are secondary metabolites produced by joint interactions between animals, microbes, and plants (Reichling, 2010). These substances do not seem to have orchestrated impact on the physiology of the plant (Jones & Dangl, 2006), but they are important for improving protection against attacksand enhance plant fitness (Stamp, 2003). Secondary metabolite production is frequently constrained to a small number of species within a phylogenetic group, as opposed to primary metabolites (lipids, proteins, polysaccharides, and amino acids), which are found throughout the plant kingdom (Hashemi & Davoodi, 2012). Furthermore, they are only produced at micro- to submicromolar concentrations during a specific developmental period of plant growth (Hashemi & Davoodi, 2012).

The major benefit of using plant-derived antimicrobials (PDAs) for therapeutic purposes is that they do not have the side effects that are frequently associated with synthetic chemicals/drugs (Van Wyk & Gericke, 2000). Furthermore, to the best of our knowledge, there is to the best of our knowledge, there is no scientific informationabout the antimicrobial resistance to these phytochemicals, this could be owing to their multiple mechanisms of actions, which may avert the variety of resistant strains of bacteria. These compounds' potent antimicrobial properties, low cost, noninvasive and nontoxic nature have led to their widespread as natural sources for the discovery and formulation of novel antibiotics in pharmaceutical industries. They are also use in human health management, herbal therapy in veterinary medicine and livestock industries, and as components of disinfectants in the food industry.

This chapter presents a comprehensive discussion on a diverse set of plant-derived antimicrobials, with a particular importance on the various biological effects these compounds have on bacterial virulence which are vital for pathogenesis in the host. The major plant compound and selected antimicrobial mechanisms were also discussed.

INFECTIOUS DISEASES

Infectious diseases are primary sources of morbidity and mortality among living organisms worldwide. They are diseases mediated by micro-organisms which arefrequently tiny in size, such as fungi, viruses, bacteria, or parasites, and are spreadeither directly or indirectly from one person to another (Oluyege *et al.,* 2010; Osuntokun *et al.,* 2018; Aladejana *et al.,* 2021). People can also become infected after coming into contact with an infected animal that is carrying a pathogenic microorganism that can infect humans (Oladele *et al*. 2020, 2021a). Disease symptoms may not appear in normal circumstances when the host's immune system is fully active. If the host immune system is impaired, or the infectious agent overwhelms the immune system, an infectious disease ensues. Bacteria, viruses, fungi, protozoa, helminths, and prions are the most common causes of infection. The World Health Organization ranked two infectious diseases (i.e. Diarrheal diseases and lower respiratory infections) in the top 10 causes of global mortality in 2019. A multitude of pathogenic pathogens can cause both of these disorders.

Infectious diseases have tormented mankind for millennia, and in certain cases, they have even influenced history. The biblical plagues, the Middle Ages' Black Death, and the 1918 "Spanish flu" pandemic are just a few instances. The 1918 influenza pandemic killed more than half a million Americans and up to 50 million people globally, and it is thought to have contributed to the end of World War I.

Epidemics and pandemics have always had significant social and economic consequences for the people who are impacted, but in today's interconnected globe, the consequences are really global. The COVID-19 pandemic, which began in 2020, has conclusively shown this (Oladele *et al*., 2020b, 2021b). Infections can quickly migrate from one location to another. A spike in cases in one place can lead to a recurrence of instances in other parts of the world until the infection can be contained globally.

Biological Agents of Infectious Diseases

The major categories of infectious agents are fungus, helminths, prion (a newly discovered class of infectious mediators), viruses, protozoa, and bacteria. Infectious agents can grow in various body compartments of a living organisms. The two major compartments are extracellular and intracellular. Extracellular pathogens are those that live on the surface or outside of cells. Organisms in this group can only replicate outside of their cells. If they are ingested by phagocytic cells in the host, they are usually killed. To stop the phagocytic process, surface molecules such as a capsule could be created. Bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa,* and *Escherichia coli* are examples of extracellular pathogens.

Intracellular pathogens must enterinto the host cells for them to reproduce, and so must either be prevented from entering cells or be detected and eliminated. Such pathogens can be subdivided further into those that replicate freely in the cell, such as viruses and certain bacteria (species of *Chlamydia* and *Rickettsia* as well as *Listeria*), and those, such as the mycobacteria, that replicate in cellular vesicles.

Bacteria

Bacteria are prokaryotic unicellular organisms that lack lysosomes, mitochondria, and nuclei, amidst other internal membrane constituents. Their genetic materials are double-stranded circular DNA with only a fraction of the protein seen in eukaryotic genomes. Majorityof bacteria replicate by binary fission and have anextensivearray of diversity, notwithstanding the commonality that brings them together in the Monera Kingdom. Bacteria are classified into five groups according to their basic shapes: spiral (spirilla), rod (bacilli), spherical (cocci), comma (vibrios) or corkscrew (spirochaetes).

Bacteria have a variety of energy sources. Some bacteria are photosynthetic, which means they get their energy from the sun. Some get their energy by oxidizing inorganic molecules, while some bacteria make energy by breaking down organic substances like amino acids and carbohydrates through a respiratory mechanism. Some bacteria (aerobes) require oxygen, while some others cannot tolerate it (anaerobes). Some bacteria can thrive in the presence or absence of oxygen (facultative anaerobes).

Bacteria are typically classified into two groups based on the content of their cell walls, which determines their Gram stain reaction. Following the staining method, Gram-negative bacteria appear pink while Gram-positive bacteria appear purple. The difference between the two groups is primarily attributed to Gram positive bacteria having a much higher peptidoglycan content (cell wall). Some common pathogenic gram-negative organisms include *Escherichia coli*, which causes diarrhea, *Salmonella typhi*, which causes typhoid fever, and *Yersini apestis*, which causes plague. *Staphylococcus aureus*, which causes skin, respiratory, and wound infections, and *Clostridium tetani*, which produces a toxin that can be fatal to humans (Oludare *et al*., 2017; Thonda *et al*., 2018).

Due to the high lipid content of the peptidoglycan, some bacteria, such as mycobacteria, cannot be properly stained. As a result, other staining procedures (Kinyoun or acid fast stain) are applied to take advantage of the resistance to staining after a longer initial staining period.

Viruses

Viruses are not organisms in and of themselves because they lack metabolism and cannot multiply without the help of a host cell, however they have been found to infect both plants and animals as well as fungi and bacteria. As obligate intracellular parasites, they rely entirely on the complex metabolic machinery of eukaryotic or prokaryotic cells to replicate. A virus's primary goal is to transport its genome into the host cell so that it can be expressed (transcribed and translated) by the host cell.

A virus particle is made up of a nucleic acid-based viral genome encased in a protein coat known as a capsid. Several viruses that attack mammals are encased in a lipid envelope that they pick up in the cell membrane of their host during their migration in the cell. In contrast with other microbes that have double-stranded DNA as their genetic material, viral genomes can be double- or single-stranded RNA (RNA virus) or double- or single-stranded DNA (DNA virus). A viral particle connects to a specific host cell via capsid or protein receptors on its outer envelope in a basic process of invasion and reproduction by a DNA virus. The viral genome is usually injected into the host cell, where it reproduces its DNA, transcribes the DNA to generate messenger RNA (mRNA), and then translates the mRNA into proteins of the virus using host cell enzymes. After the DNA and viral proteins have been reproduced, the new viruses are formed into full viral particles and exit the host cell. Virus-mediated enzymes can sometimes destroy the host cell by damaging the cell membrane and discharging newly synthesized virus

particles. In some situations, additional virus particles depart the cell through a budding process which weakening but not killing the cell.

Replication of certain RNA viruses are different in that their genetic material could be used as messenger RNA to synthesized the virus proteins, with a particular viral RNA polymerase copying the RNA template to produce the genome for the newly synthesized viral particles. RNA viruses known as retroviruses transcribe the RNA genome into DNA using a special enzyme called reverse transcriptase. The DNA subsequently integrates into the genome of the host cell. Long dormant periods are common in these viruses, during which their genetic materials are reliably reproduced and spread to daughter cells every time the cell divides. A well-known illustration of a retrovirus is the human immunodeficiency virus (HIV), which causes AIDS.Viruses, like other infectious agents, create illness by interfering with normal cell activity. They accomplish this in a number of ways. Some viruses produce repressor proteins that prevent the creation of proteins, RNA, and DNA in the host cell. Cell membranes and lysosomal membranes may be weakened by viral activity, resulting in cell autolysis. Some viral proteins are harmful to cells, and virus-infected cells may be killed by the body's immune system. Viruses are categorized with reference to their mechanism of replication, genome structure, chemical makeup, form and size. Many pleomorphic and filamentous viruses have helical morphology in their nucleocapsids. A helical array of capsid proteins (protomers) wraps around a helical filament of nucleic acid to form helical nucleocapsids. The nucleocapsids of many "spherical" viruses have an icosahedral shape. Recognition, classification and documentation are enhanced by the arrangement and number of capsomeres. An outer envelope is found on many viruses.

Retroviruses which cause AIDS and various types of cancer; rotaviruses which cause gastroenteritis; rhinoviruses which cause most common colds; poxvirus which causes smallpox, and herpes viruses which cause painful vaginal lesions, cold sores, and chicken pox, are examples of DNA viruses. paramyxoviruses and myxoviruses which cause mumps, measles, and influenza; are all types of RNA viruses that induce diseases in human.

COVID-19, a newly discovered infectious disease caused by the virus SARS-CoV-2, became the leading cause of death in 2020 (Oladele *et al*., 2021c). COVID-19 was recognized as the third largest cause of death in the United States in 2020, behind heart disease and cancer, according to statistics analyzed by the Centers for Disease Control and Prevention (CDC).

Fungi

Fungi are heterotrophic eukaryotic organisms with chitin-based or rigid cellulose cell walls that replicatechieflyby formation of spore. Whilesome fungus including yeasts are unicellular, the majority of them are multicellular. Fungi can take the shape of yeasts or molds, and they can switch between the two depending on the environment. Yeasts are small cells with a diameter of 3 to 5 micrometers. Molds are made up of 2 to 10 micrometre-wide filamentous branching structures called hyphae, which are made up of numerous cells laying end to end. Fungi, together with bacteria act as decomposers and play significantrole in the environment.

Animals and plants can both be infected by fungus. Mycoses are fungal illnesses that affect people and include conditions including blastomycosis, coccidioidomycosis, and histoplasmosis. These illnesses might be benign, such as an upper respiratory infection, or severe, affecting the bloodstream and all organ systems. Fungi can cause serious illness in people whose immune systems have been compromised by hunger, cancer, or the use of immunosuppressive medicines. Antifungals, a type of antibiotic,

are beneficial in the treatment of fungal infections. In a healthy person, many fungal infections, such as athlete's foot and yeast infections, are not hazardous. People with weakened immune systems (as a result of disorders like HIV or cancer) are more susceptible to fungal infections.

Fungal infections can affect only one area of the body (localized) or many areas of the body (systemic). Localized fungal infections usually affect the skin and nails, the vaginal area, or the mouth, and they can afflict persons with a healthy or impaired immune system. When the regular balances that keep fungi in check are disrupted, localized fungal infections can arise. Certain forms of fungus (such as Candida) are naturally found on human surfaces and in the intestine. The bacteria that ordinarily live in the digestive system and vaginal area inhibit the growth of these fungi. Antibiotics can destroy beneficial bacteria, allowing fungus to proliferate unchecked. The proliferation of fungi that results can produce symptoms, which are usually minor. The balance is restored when the bacteria grow back, and the condition normally goes away. Systemic fungal infections can damage the skin as well as organs such as the lungs, eyes, liver, and brain. They are most common in those with a compromised immune system.

Fungal infections that take advantage of a weakened immune system are known as opportunistic infections. As a result, they are more common among persons who have a weaker immune system, such as those who have AIDS or who are using immune-suppressing medicines. Opportunistic fungal diseases are seen all over the world. The following are examples of common opportunistic fungal infections: Candidiasis, Mucormycosis, and Aspergillosis, Opportunistic fungal infections can be extremely aggressive, swiftly spreading to other organs and frequently resulting in death.

Antifungal medications can be used to treat a fungal infection on the skin or another surface, such as the vaginal area or the inside of the mouth. When treating more serious infections, antifungal medications can be administered orally or intravenously. Several months of treatment are often required for serious infections.

Protozoa

Protozoa are heterotrophic unicellular eukaryotic organism including that include paramecium and amoeba. Their cell comprises a nucleus and other cell organelles similar to animal and plant cells, and bigger than bacteria. Due to the absence of cell walls in protozoa, they couldexecute anextensivevariety of flexible and quick motions. They could be contracted by being bitten by an infected mosquito, or by ingestion contaminated water or food.

Protozoa are divided into four categories or classes. Intracellular parasites, flagellates (which travel using a tail-like structure), amoebas (which move using pseudopods or a transient cell body projection), and ciliates (which move using hair-like structures called cilia).

Malaria, a tropical disease that is responsible for more than 300 million cases of disease annually, is caused by many species of *Plasmodium* (a protozoan). *Giardia* and toxoplasmosis are other examples of protozoan infections. Depending on the protozoa a healthcare provider suspects, blood tests, stool tests, or biopsies may be used to diagnose protozoan infection. Treatment depends on the underlying cause.

Helminths

Helminths are parasitic worms that feed on their hosts. They are the most frequent infectious agents in humans in underdeveloped nations, causing a worldwide illness burden that exceeds that of more well-known diseases such as malaria and tuberculosis. Helminths are invertebrate animals that are infectious

parasites in some cases. They have distinct tissues and are multicellular. Their physiology is comparable to human in certain aspects because they are animals. Because medications that terminates helminths are typically harmful to mammalian cells, parasitic helminth infections are complicated to treatment. Roundworms, tapeworms, and flukes are the three main types of worms found in the human body.

Humans are infected by roughly 300 different helminths. Helminths are primarily transmitted through direct contact with the parasite or ingestion of contaminated food or water. The parasites can enter through human skin from infected water or soil in some situations. Many helminths have complicated reproduction cycles with numerous phases, many of which necessitate the presence of a host. The flatworm Schistosoma produces the minor ailment swimmer's itch in the body. Schistosomiasis is endemic in 70 countries, affecting approximately 200 million people, the majority of whom live in impoverished communities with little access to safe drinking water or proper sanitation. Up to 20 million people in Sub-Saharan Africa are infected, with 90 percent of those infected suffering from severe chronic health implications. In freshwater, schistosome eggs develop, and the larvae infect snails. The larvae cling to and pierce human skin when the snails shed their larvae. They mate, grow, andfeed in the human circulatory system, causing sickness symptoms such as diarrhea and abdominal pain due to the impairmentof human tissues (liver and spleen) induced by the amassing schistosome eggs with their sharp spines.

Trichinella spiralis(roundworm) is another helminth illness that causes Trichinosis. This infectious pathogen is commonly found in infected animals' badly cooked meat. Early disease symptoms include fever, diarrhea, and vomiting; and later caused acute muscle pain because the larvae grow and mature in tissues. Congestive cardiac failure and respiratory paralysis are common in fatal instances.

Flukes are helminths that dwell in the spleen, liver, lungs, and intestines, among other places in the body. Freshwater snails serve as intermediary hosts in the life cycle of these worms. The larval worms can enter people by contact with the skin after the snail releases larval forms of the worm into fresh water. The parasites pass out of the body without causing any symptoms in the majority of cases of fluke infection. Nevertheless, reinfection is possible. If it happens on a systematic basis, it might damage the body's organs. Fever, chills, coughing, muscle aches, itching, and rash are common symptoms of infection in symptomatic patients. Flukes can infiltrate the spinal cord, brain, lungs, orliver in severe infections. Vermifuges, which are anti-worm medications that successfully kill parasitic worms, can be used to treat most infections. Certain helminth infections can be healed quickly, others can take months or years to resolve, and patients may be left with crippling disability as a result of organ and limb damage.

Helminth infection can be avoided in a number of ways. To begin, avoiding contact with the parasites. Hand washing, keeping a clean bathroom and kitchen, and avoiding contact with infectious animals can all help to prevent exposure. Furthermore, thoroughly cooking food, especially pork and beef that may contain parasites, inhibits parasite intake. Parasites are prevented from being consumed by chlorinating, filtering, or boiling drinking water. To avoid parasite uptake while bathing or swimming in infected water, which is an issue for fluke parasites in particular, water can be boiled or avoided entirely. Lowering the prevalence of helminths in a population is another strategy to avoid infection. This is accomplished through deworming or the giving of anti-worm medications to affected people on a regular basis. This can effectively diminish the parasite's long-term impacts on infected people as well as the parasite's prevalence within a population. Communities can be educated about hygiene, sanitation, and correct food preparation in order to effectively apply prevention techniques in communities impacted by helminth infections. These strategies, when combined with helminth therapies, serve to lower the prevalence and consequences of helminths in communities.

Prions

Manydeteriorating illnesses of the central nervous system have been connected to infectious agents made entirely of protein over the last two decades. These "proteinaceous infectious particles" are known as prions (preeons). Prions are a type of protein that can be found in two different states: normal and misfolded. Prions that have been misfolded have been related to brain illnesses such mad cow disease (bovine spongiform encephalopathy) and human Creutzfeldt-Jakob disease. Prion proteins are principally proteins lacking any genetic material and their mode of action is substantially different from that of viruses and bacteria. When a misfolded prion infects a healthy person (perhaps through infected food), it changes properly folded proteins into the disease-associated version. Some prion illnesses are inherited; others are thought to be contracted through ingestion of diseased tissue or through surgical treatments such as tissue transplants. All of the known prion disorders cause brain tissue to be riddled with holes, however not all prions cause disease.

Transmissible spongiform encephalopathies (TSE) and genetic or sporadic disorders (GSD) are the two types of Prion. These diseasesinvolve the development of both normal prion (PrP) and abnormal prion (PrP(sc)) which varies from PrP in forming tertiary structure rich in beta-sheets. PrP(sc) is, in fact, a completely dehydrated protein with an anhydrous environment and a narrow carbon dioxide gas gap explains why it appears to be resistant to proteases, chemical disinfectants in water phase (unless in particular conditions), heat, and radiation. The incubation period, primary symptoms, and type of CNS lesions varies between GSD and TSE disorders. Other animal prion diseases include scrapie and kuru.

PLANT-DERIVED COMPOUNDS AND NATURAL PRODUCTS WITH ANTIMICROBIAL PROPERTIES

Antimicrobial peptides (AMPs)

Antimicrobial peptides (AMPs) are short biomolecules (proteins) of approximately 5 to 50 amino acids with antimicrobial action (Van Moll *et al*., 2022). They are made up of polar, non-polar, and positively charged residues with net charges ranging from +2 to +1. Microbicidal activity is dependent on the cationicity and hydrophobicity of AMPs. The non-polar residues form a unique complex with the polar residues fostering their membrane insertion (Ebenhan *et al.,* 2014). AMPs have evolved into effective alternative anti-infective in recent decades, addressing the need for novel candidate molecules in mitigating emerging trend antibiotic resistance. Furthermore, recent epidemics and pandemics have enhanced the appeal of these bioactive peptides in treating the new appearance of microbial diseases (Erdem Büyükkiraz &Kesmen, 2022). By primarily targeting membrane or key intracellular components, antimicrobial peptides curb a wide spectrum of bacteria in various and unique ways (Lie *et al*., 2021).

AMPs are made in diverse hosts via recombinant technologies aside from being naturally sourced (Erdem Büyükkiraz & Kesmen, 2022). Their synthetic analogs have recently been expected to overcome the stability, toxicity, and activity constraints associated with natural AMPs (Lima *et al.,* 2021; Gouveia *et al*., 2022; Vanzolini *et al*., 2022). Plants and insects use AMPs as antibiotics to defend themselves againstpossiblyhazardous microorganisms, while microbes also produce AMPs to sustain their niche in the environment (Van Moll *et al*., 2022; Babich *et al*., 2022). AMPs are also known as 'host defense peptides' in higher eukaryotic organisms, stressing their immunomodulatory properties (Guryanova, &

Ovchinnikova, 2022). These activities vary depending on the type of AMP, but they all involve cytokine and growth factor-like effects that are important for immunological homeostasis. In humans, LL-37 elicited impressive immune-modulatory effects by attracting monocytes and encouraging the generation of numerous chemical messengers to drive inflammatory processes (Agier *et al*., 2015).

Antimicrobial proteins and peptides produced by microorganisms such as bacteriophages have potent antibacterial action (Rodríguez-Rubio *et al*., 2013; Yan *et al*., 2014). Phage lysins are peptidoglycan-hydrolyzing enzymes that are 25 to 40 kDa in size (Fischetti, 2008). By digesting peptidoglycan, this AMP weakens the bacterial cell wall, allowing phage progeny to exit through perforations in the cell wall. (Ha *et al*., 2018; Plotka *et al*., 2019). Their effects on a variety of Gram-positive and Gram-negative bacteria have been studied (Salas *et al*., 2020). PK34 and LysAB2 P3 are two respective examples of antibacterial proteins that are toxic to *Mycobacteriumtuberculosis* and *Acinetobacterbaumannii* (Peng *et al*., 2017). PlyV12, a phage lysin, was also reported to possess anti-bactericidal potency against specific Gram-positive bacteria (Yoong *et al*., 2004). VAPGHs (virion-associated peptidoglycan hydrolases) are active against Gram-positive and Gram-negative bacteria. Bacteriophage vB SauS-phiIPLA88, for example, produces HydH5 and is effective against *Staphylococcus aureus* (Rodríguez *et al*., 2011). Similarly, the *Xanthomonas oryzae* phage Xop411 protein gp21 has lethal action against the *Xanthomonas* genus as well as the Gram-negative bacteria *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa* (Weng *et al*., 2018). Polymyxins are lipopeptide antibiotics obtained from *Paenibacillus polymyxa* (Stansly *et al*., 1947), unlike phage AMPs. They are made up of a cyclic heptapeptide with a tripeptide side chain and a fatty acyl tail at the N-terminus (Velkov *et al*., 2019). Gram-negative bacteria such as *Enterobacterales, A. baumannii, P. aeruginosa,* and *S. maltophilia* have been found to be susceptible to these peptides (Velkov *et al*., 2019). Mechanisms of action includes membrane disruption and interactions (Sampson *et al*., 2012).

In certain cases, irregularexpression of AMP could lead to autoimmune disorders, stressing the consequence of better understanding these molecules and their complicated functions (Zhang & Gallo, 2016). These proteins have anextensivearray of activities, such as the ability to terminate viruses, fungus, yeasts, bacteria, and even cancer cells directly (Zhang & Gallo, 2016; Dijksteel *et al*., 2021). Antimicrobial activity of the human cathelicidin LL-37 is quite pronounced (Shurko *et al*., 2018). In fact, antifungal and antiviral activities of the same AMP have also been reported. Bergman *et al*. (2007) discovered this peptide reduces HIV-1 proliferation, while Luo *et al*. (2019) reported its direct toxicity against *Aspergillusfumigatus* infection. FK-13 was identified as the smallest peptide active against human immunodeficiency virus (HIV) among 15 human cathelicidin LL-37-derived peptides by Wang *et al*., (2008), while GI-20 had the greatest therapeutic index, which was double that of LL-37. The therapeutic index of BMAP-18, which is generated from bovine cathelicidin BMAP-27, was equivalent to that of GI-20.

The arrangement of peptides, helical shapes, and aromatic residues all have a role in HIV inhibition. Lactoferrin (LF), one of the AMPs, is an iron-binding glycoprotein found in a variety of mucosal secretions and has recently been shown to exhibit antiviral activity against the SARS-CoV virus. Because of its powerful antiviral properties, LF could be used as an immunity booster, a medication, or a drug combination with conventional antivirals (Elnagdy & AlKhazindar, 2020). Chianese *et al*. (2022) recently revealed antiviral activity of AR-23, a peptide derived from *Rana tagoi* secretion, against both DNA and RNA viruses, enveloped or not. According to their findings, AR-23 had a higher inhibitory action against both DNA (HSV-1) and RNA (MeV, HPIV-2, HCoV-229E, and SARS-CoV-2) encapsulated viruses in the early stages of infection.

Lectins

Lectins are biologically diverse (glyco-)proteins with antibacterial properties, particularly against bacteria, fungus, and protozoa, as well as the ability to modulate host immunity (Swarna *et al*., 2021). They do this by binding carbohydrates to pathogen surfaces, which can harm the cell membrane and prevent germs from attaching to host cells (Carneiro, *et al*., 2021; da Silva *et al*., 2022). Because these proteins are ubiquitous in nature, they are generally classified based on their natural source. Alternatively, they are classified according to their binding specificity to certain sugars/ glycol-moieties, which are mediated by key molecular interactions (del Carmen Fernández-Alonso *et al*., 2013; Liu *et al*., 2019). Furthermore, some lectins require the presence of certain divalent metals, such as Calcium and magnesium ionsto bind to their specific carbohydrates (Vasta *et al*., 2012)

Plant lectins are well researched regarding their microbial toxicitysuggesting they could be employed in medication development (Fonseca *et al*., 2022). Ferreira *et al*. (2018) reported the immunomodulatory lectin from *Alpinia purpurata* inflorescence exhibited bacteriostatic and fungistatic properties against non-resitant and oxacillin-resistant strain of *Staphylococcus aureus*, *Candida albicans* and *Candida parapsilosis*. The 54 kDa lectin from Chenopodium album seeds (CaLec) inhibited two harmful bacterial strains, *S. aureu*s, and *Escherichia coli*, according to Javed *et al* (2022). Antibacterial activities of *Schinus terebinthifolius* leaf lectin against *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella enteritidis* and *Staphylococcus aureus*have been reported, with the protein showing both bacteriostatic and bactericidal properties towards test microbes (Gomes *et al*., 2013). In addition to their antibacterial properties, the lectins legume lectins from the Egyptian varieties of *Vicia faba, Lens culinaris*, and *Pisumsativum* elicited potent antifungal activities against *C. albicans*. A 75-kDa galactose-binding lectin from Euphorbia antiquorum L (EantH) was found to have lethal activities against Staphylococcus aureus, Staphylococcus epidermidis, Samonella typhimurium, Propionibacterium acnes, and Streptococcus agalactiae by interacting with the galactose moiety of bacteria cell walls in a recent study (Siritapetawee *et al*., 2018)

The antiviral and virucidal effects of a banana lectin (BanLec) against cattle viral diarrhea virus and bovine alphaherpesvirus type 1 were reported by de Camargo *et al*. (2020). The viral titer and vitality of susceptible Madin-Darby Bovine Kidney cells (MDBK) treated with BanLec before and after viral infection were measured to determine its antiviral activity. BanLec's virucidal properties were determined by incubating the lectin with the viruses before measuring the viral load in exposed cells. Treatment with 25 µg/mL BanLec resulted in high levels of inhibition against BVDV-1 (99.98%) and BoHV-1 (99.68%) without altering cell viability, indicating that BanLec has promising antiviral potential. According to the findings of Wang *et al.* (2021), the lentil lectin from *Lens culinaris* which binds to oligomannose-type glycans and GlcNAc at the non-reducing end terminus, was found to have effective and wide-ranging antiviral activity against a host ofvariants and mutant strains, such as artificial N-/O-linked glycosylation site mutants, naturally existing amino acid mutants and epidemic variants of SARS-Cov-2. Similarly, the potency of an N-acetylglucosamine (NAG)-binding lectin (TCLL) from Tamarind against cellular invasion and entry of alphavirus have been reported by Kaur *et al* (2019). Gondim and colleagues (Gondim *et al*., 2019) also reported the lectins from specific Brazilian legumes- *Canavalia brasiliensis*, *Canavaliamaritima*, *Diocleasclerocarpa*and *Dioclea lasiocarpa*, and algae- Amansia multifida (AML), *Solieria filiformis, Meristiella echinocarpaHypnea musciformis*, and *Bryothamniom seaforthii*showed impressive antiviral activities against diverse pathogenic viruses including HIV, influenza, and feline coronavirus via diverse mechanisms, particularly by preventing viral entry into their hosts. Aside from

the toxicity of lectins to animal viruses, specific lectins have also been reported to interfere with the activities of plant viruses. Bilal *et al* (2020) reported the antiviral activity of lectin from *Crocusvernus* corm against Potato virus Y by targeting specific viral genes.

Ribosome-inactivating proteins (RIPs)

Ribosome-inactivating proteins (RIPs) are toxic N-glycosidases that depurinate rRNAs in both eukaryotes and prokaryotes, halting protein synthesis during translation. RIPs can be discovered in a wide variety of plant species and tissues. Antifungal, antibacterial, and antiviral properties of these quintessential proteins have been reported (Zhu *et al*., 2018). Ajji *et al.* (2018) reported a type 1 RIP named balsamin from *Momordica balsamina* in addition to inhibiting the replication of HIV-1 also inhibited the growth of *S. epidermidis, S. aureus*, *S. enterica* and *E. Coli* in a dose-dependent manner. Similarly, the RIPs ME1 and ME2, isolated from *Mirabilis expansa* roots have also been reported to be toxic to a wide range of fungal pathogens, including *Fusarium* and *Trichoderma* species (Priyanka *et al*., 2013). Quinoin was recently reported to totally abolish viral infection of Tobacco Necrosis Virus (TNV) at nanomolar concentrations while also inhibiting the growth of Pseudomonas syringae pv phaseolicola and Pseudomonas syringae pv actinidiae (Ragucci *et al*., 2021). The authors in this study concluded the antiviral activity of this type 1 RIP based on both inhibitions of protein synthesis and depurination of the viral genome. Corroboratively, Bouganin a 28 kDa protein from n from Bougainvillea spectabilis Willd decreased the pathogenicity of Zucchini yellow mosaic virus (ZYMV) while showing potent antifungal activity for *Rhizoctonia solani*, *Trichoderma harzianum,* and *Fusarium oxysporum* at tested concentrations (Güller *et al*., 2018). Aside from type-1 RIPs, type 2 RIPs have also been reported to elicit impressive anti-pathogenic bioactivities (Park *et al*., 2009). Pebulin, a type 2 RIP elicited potent antifungal activity by inhibiting the growth and germination of *Alternariasolani* and *Fusariumoxysporum* spores (Rezaei-Moshaei *et al*., 2021).

MECHANISMS OF ANTIMICROBIAL ACTIONS OF PLANT-DERIVED COMPOUNDS AND NATURAL PRODUCTS

Suppression of Toxin secretion

Microbial poisons are chemical composites that are essential for pathogenesis and virulence in the host, making them ideal objectives for curativetreatments. Endotoxins (released after bacterial lysis) and exotoxins (secreted by bacteria) and are examples of microbial toxins, however mycotoxins are poisonous metabolites secreted by fungi with variousbiological actions and chemical properties that mediated a diversity of diseases in humans. Antibiotics have traditionally been used to treat bacterial infections; however, using antibiotics to terminate toxigenic microbes has some drawbacks, including disruption of normal microbiota (Jernberg *et al*., 2010), higher pathogenesis due to amplified toxin manufacture and cell lysis, as seen in E. coli O157:H7 (Walterspiel *et al*., 1992; Wong *et al*., 2000), and resistance development (Rasko & Sperandio, 2010). Furthermore, even after bacterial clearance, toxin-facilitated pathogenesis can persist in the host (Burnett *et al*., 2005). As a result, antibiotics in over-all are inadvisable to be used in the treatment of toxigenic organisms, and it is preferable to use a substitutetreatment to combat pathogens' toxin-facilitated virulence.

Extracts of medicinal plants and their active molecules have previously been shown to be significantly suppressed fungal toxins produced by Aspergillus spp andbacterial toxins secretionby *E. coli*, *S. aureus,* and Vibrio spp. For instance, a plant-derived dihydroisosteviol, has been shown to suppress cholera toxin-facilitated intestinal fluid secretion (Pariwat *et al*., 2008). Plant polyphenols like RG-tannin and apple phenols have been shown to inhibit DPribosyltransferase activity, which is required for cholera toxin action (Morinaga *et al*., 2005). The toxin-mediated fluid accumulation in mouse ileal loops was also reduced, according to the researchers. Extracts from spices such as white pepper, sweet fennel, andred chilli have been documented to significantly suppress the secretion of cholera toxin in research by Yamasaki *et al* (2011). Capsaicin was a significant constituentpresent in the samples which markedly decreased the expression of main *V. cholerae* virulence genes such as toxT, tcpA, and ctxA. Likewise, eugenol, a clove essential oil, has been documented to markedly decreasethe production of *S. aureus-hemolysin*, toxic shock syndrome toxin 1, and enterotoxins (SEA, SEB) (Yim *et al*., 2011). A decrease in the expression of some virulence genes (hla, tst, seb, and sea) implicated in different aspects of *S. aureus* toxin secretionhas been discovered through transcriptional analysis. Also, 4-hydroxytyrosol, an olive compound, has been demonstrated to effectively inhibit*in vitro* production of *S. aureus* endotoxin (Friedman *et al*., 2011).

Enterohemorrhagic *E. coli* (EHEC) is the causative agent of chronic human infections such as hemorrhagic uremic syndrome and hemorrhagic colitis (Welinder-Olsson & Kaijser, 2005). Extraction products of *Curtisia dentata*have been reported to suppressproduction of the vtx1 and vtx2 genes in Enterohemorrhagic *E. coli* in a study conducted by Doughari *et al*. (2012). This plant's extracts have traditionally been used as an antidiarrheal agent (Noten, 2004). Other plant extracts with similar verotoxin inhibitory activity include *Haematoxylon brasiletto* (Heredia *et al*., 2005), *Jussiaea peruviana* L., *Salvia urica* Epling, *Cupressus lusitanica*, and *Limonium californicum* (Boiss.) (Sakagami *et al*., 2001). Shiga toxins have been inactivated by antitoxin antibodies (Krautz-Peterson *et al*., 2008), as well as by someartificialpeptide and carbohydrate molecules formulated to have high affinity for the active site of receptor sites on cell membranes (Kitov *et al*., 2008).

Anti-Shiga toxin-2 activity of extracts of grape pomace and grape seed has been discovered by Qui˜nones *et al*. (2009), thus providing cellular defense against Shiga toxin-2. Similarly, extracts of green tea, hop bract, daio (*Rhei rhizoma*), andapple have been documented to exhibit inhibition against Shiga toxin secreted by E. coli O157:H7 (Oi *et al*., 2002).

In humans and animals, mycotoxins (aflatoxins)secreted by *Aspergillus pseudotamarii, A. bombycis, A. tamari, A. nomius, A. parasiticus,* and *A. flavus* could cause toxicity that could be either acute or chronic (Kurtzman *et al*., 1987). Cottonseed, corn grain, peanuts (Sur & Celik, 2003), rawmilk (Hussain & Anwar, 2008), cheese (Ertas *et al*., 2010), canned mushrooms (Kamal *et al*., 2009), chicken meat (Resanovic *et al*., 2009; Ertas *et al*., 2010), and pork (Harvey*et al.,* 1989) are all food items commonly connected with mycotoxicosis. Several studies have shown that essential oils can reduce mycotoxin production. Clove, carrot, and garlic crude aqueous extracts have been demonstrated to exhibit marked suppressive action against secretion of aflatoxin in rice (Thanaboripat *et al*., 1997). The pungent and coloring constituent of red chilli (*Capsicum annum*), capsaicin and capsanthin, and essential oils of some medicinal plants such as thymol, nerol, geraniol, cinnamaldehyde, and citronellol have been reported to effectively suppress both *A. flavus*toxin secretion and growth (Masood *et al*., 1994).

Clove and cumin oils were found to have toxin-inhibitory effects in *A. parasiticus* (Farag *et al*., 1989), with aflatoxin production reduced by 99%. Similar results were obtained with essential oil derived from wild thyme against ochratoxin-producing aspergilli. Ochratoxin production was decreased by actions of

essential oils from wild thyme by more than 60% (Sokoli´c-Mihalak *et al*., 2012). Similarly, *Curcuma longa* essential oil and curcumin were found to retard the production of *A. flavus* toxin (Ferreira *et al*., 2013). Furthermore, spore germination which enhance production of toxins in *Aspergillus* sp. was markedly suppressed by essential oils (Gemeda *et al*., 2014).

Modulation of Bacterial Virulence

At different phases of infection to cause disease, there are expression of multiple virulence factors which mediate the pathophysiology of microbial infection in a host. Infections in humans could be controlled by reducing the production of these virulence factors. Elucidation of the major virulence mechanisms of pathogenic bacteria has been accomplishedvia significant advances in comparative genomics, transcriptomics, and proteomics (Aladejana *et al*., 2021b,c). As a result, virulence features are primary focus for vaccine development and treatment of infections (Taylor & Roberts, 2005). In many microorganisms, quorum sensing regulates the expression of genes encoding various virulence factors (Antunes & Ferreira, 2009; Novick & Geisinger, 2008).

Many sources of evidence indicated that plants secrete antiquorum sensing phytocompounds that disrupt cell-to-cell interactions, lowering virulence genes expression in pathogens. Trans-cinnamaldehyde has previously been shown to reduce the expression of luxR, which codes for a transcriptional regulator of quorum sensing in *C. sakazakii* (Amalaradjou & Venkitanarayanan, 2011). Also, Bodini and colleagues discovered that 'garlic extract and p-coumaric acid inhibited quorum sensing in quorum sensing reporter strains, indicating that plant compounds may modulate virulence in microbes by influencing quorum sensing'. Invasion and adhesion to intestinal epithelium are vital for infection and virulence in the majority of enteric pathogens. In various microbes, specific proteins aid in adhesion and invasion. Inl A and Inl B, for example, are surface proteins that facilitate L. monocytogenes receptor-facilitated entrance into intestinal cells (Portnoy *et al*., 1992). Several plant-derived antimicrobials have demonstrated reduction of various virulence features in some food-borne toxins including uropathogenic *E. coli*, *L. Monocytogenes*, (Amalaradjou *et al*., 2011), and *Salmonella enterica serovar Enteritidis*by suppressing the expression of virulence genes. Furthermore, when *K. pneumoniae* is exposed to plant-derived antimicrobials, it produces fewer capsules, which modulates its survival and virulence in the host (Derakhshan *et al*., 2008). These findings highlight ability of phytochemicals to effectivelymitigate virulence features that are vitalin the pathobiology of the infections and enhance the discovery of new therapeutics for microbial virulence treatment.

Enhancement of Antibiotic Susceptibility in Drug Resistant Bacteria

As awareness of antimicrobial resistance mechanisms in pathogens grows, multifaceted approaches to reversing bacterial antibiotic resistance and combating infections are being investigated. Scientific reports have documented plant-derived antimicrobials as possible resistance modulating phytochemicals corroborating their inherent antimicrobial properties. Brehm-Stecher & Johnson (2003) found that low doses of sesquiterpenes like apritone, bisabolol, andnerolidol enhanced sensitivity of bacteria to a variety of antibiotics like vancomycin, tetracycline, clindamycin, and ciprofloxacin. Interestingly, extracts prepared from *Microglossa pyrifolia, Securinega virosa*, and*Mezoneuron benthamianum* plants enhanced the susceptibility of *Microsporum gypseum,* and *Trichophyton spp.* which are the key drug resistant fungi as well as bacteria like *S aureus, P. aeruginosa, Klebsiella* spp*.,* and*Salmonella* spp.to

norfloxacin (Dickson *et al*., 2006). Furthermore, geraniol (found in *Helichrysum italicum* essential oil) was reported to restore the efficacy of quinolones, chloramphenicol, and -lactams against multidrug resistant pathogens such as *Acinetobacter baumannii* (Lorenzi *et al*., 2009). Antibiotics and other medicinal plant extracts, such as *Camellia sinensis* (Aquil *et al*., 2005), *Caesalpinia spinosa* (Kondo *et al*., 2006), *Croton zehntneri* oil (Rodrigues *et al*., 2009), carvacrol (Grande *et al*., 2007), and the bioactive compound in *Scutellaria baicalensis*(baicalein) (Chan *et al*., 2011), showed similar synergism. This potential therapeutic activity of these plant bioactive compounds could be attributed to the modulation of three major resistance approaches used by drug-resistant pathogens to subdue antibiotic activities, namely enzymatic degradation of antibiotics (Davies, 1994), alteration of antibiotic target site (Spratt, 1994), and efflux pumps (Nikaido, 1994). Moreover, recent studies suggest that combining antibiotics with plant-derived antimicrobials inhibits several targets in different mechanisms/approaches vital for the virulence or normal functioning of the bacterial cell.

The production of B-lactamase enzymes is one example of a microbial strategy that contributes to resistance to B-lactam antibiotics (Frere, 1995). Numerous plant compounds with B-lactamase inhibitory activity have been identified (Jiminez-Valera *et al*., 1987). Gangou'e-Pi'eboji *et al* (2007) screened medicinal plants from Cameroon and discovered that extracts from *Garcinia lucida* and *Bridelia micrantha* inhibited B-lactamases significantly. Likewise, epigallocatechin gallate was discovered to enhance the antimicrobial activity of sulbactam and ampicillin against Methicillin resistant *S. aureus* (MRSA) by improving *S. aureus* sensitivity to penicillin and suppressing activity of penicillinase (Zhao *et al*., 2002).

Plant-derived antimicrobials have been shown in numerous studies over the last two decades to be effective efflux pump mitigators against some pathogens "gram-positive microbes" (Cherigo *et al*., 2008). Additional setbacks were initiated by gram-negative bacteria due to the presence of AcrAB-TolC pumps (potent efflux pumps) (Piddock, 2006). Eugenol, thymol, carvacrol, -resorcylic acid, and trans cinnamaldehyde, or their combinations, have been documented to enhance*Salmonella enterica serotype Typhimurium phage type* DT104 sensitivity to five antibiotics in a recent study (Johny *et al*., 2010). Because the mechanism of antimicrobial resistance in *Salmonella Typhimurium* DT104 is primarily mediated by interactions between specific antibiotic transporters and the AcrAB-TolC efflux pump, the aforementioned plant compounds may act by modulating these efflux pumps to enhance the pathogen's antibiotic sensitivity (Quinn *et al*., 2006).

Suppressing the Formation of Bacterial Capsule

Many pathogenic bacteria, including *Streptococcus pneumonia* (Hyams *et al*., 2010), *S. aureus* (O'Riordan & Lee, 2004), *K. pneumoniae* (Moranta *et al*., 2010), and *Bacillus anthracis* (Ezzell & Welkos, 1999), use polysaccharide capsules as virulence determinants (Moxon & Kroll, 1990). It shields bacteria from phagocytosis (Hyams *et al*., 2010), increasing bacterial survival within the host (O'Riordan & Lee, 2004). Furthermore, the presence of a capsule in the environment promotes bacterial adhesion, biofilm formation (Potera, 1999) and plant pathology. *Pseudomonas solanacearum* capsular polysaccharide, for example, was discovered to induce plant death by obstructing xylem vessels (Denny & Baek, 1991). Because salicylic acid is participated in plant defense signaling (Shah, 2003), Scientific reports have looked into how salicylic acid (Alvarez *et al*., 2010) or its derivatives including sodium salicylate (Domenico *et al*., 1990), bismuth subsalicylate (Domenico *et al*., 1991), and bismuth dimercaprol (Huang & Stewart, 1999), affect bacterial capsule production. These compounds were found to be beneficial in marked reduction of formation of capsules in *S. aureus* by mitigating the activity of capsular synthesisprocedures.

Moreover, beneficial activities of these compounds against various antibiotics' sub-MICs and MICs have been reported (Farzam & Plotkin, 2001). As a result, phytochemicals have been proposed as alternative native sources for the design and discovery of therapeutics that target bacterial capsule formation.

Antibiofilm Activity

Bacterial biofilms are surface-associated microbial communities encased in an exopolysaccharide matrix produced by the bacteria (Davey & O'Toole, 2000). They are a major source of concern, particularly in the hospital settings and food industry, because they are resistant to frequently used disinfectants and antimicrobials (Flemming & Wingender, 2010), leading to disorders and sicknesses such as indwelling device-mediated infections, cystic fibrosis, andendocarditis (Costerton *et al*., 1999).

Wide-rangingstudies into the possibility of alternative approaches for microbial biofilm modulation has revealed the potency of some plant-derived antimicrobials in mitigating biofilm productions in somemicrobes such as *Listeria monocytogenes* (Upadhyay *et al*., 2013), *Staphylococcus aureus* (Al-Bakri *et al*., 2010), *Pseudomonas aeruginosa* (Cheng *et al*., 2009), *Escherichia coli* (Grudniak *et al*., 2011), and *Klebsiella pneumoniae* (Derakhshan *et al*., 2010). Trans-cinnamaldehyde has been documented to mitigate formation of biofilm and incapacitate mature biofilm of *Cronobacter sakazakii* on stainless steel surfaces, urinary catheters, and feeding bottle coupons (Amalaradjou & Venkitanarayanan, 2011). Similarly, terpenes like geraniol, thymol, and carvacrol, as well as essential oils like *Syzygium aromaticum*and *Cymbopogon citratus*demonstrated significant antibiofilm activity against fungal (Khan & Ahmad, 2012) and bacterial biofilms (Knowles *et al*., 2005) found in biomedical settings and food processing environments.

Plant-derived antimicrobials, like antibiotics (Yim *et al*., 2011), have been shown to modulate bacterial gene transcription at subinhibitory concentrations (SICs, concentrations that do not inhibit microbe growth) (Amalaradjou & Venkitanarayanan, 2011), which could corroborate their antibiofilm effect. Trans cinnamaldehyde was reported to influence the transcription of genes vital for biofilm attachment, motility, formation, and quorum sensing in *C. sakazakii* (Amalaradjou & Venkitanarayanan, 2011). Similarly, Brackman *et al*. (2008) discovered that trans cinnamaldehyde inhibited the growth of Vibrio spp. biofilms. Trans-cinnamaldehyde was found to be effective at reducing biofilm formation and autoinducer 2-based quorum sensing without mitigating growth of bacteria, most likely because of its action on gene transcription. Comparable transcription influencing activity have been reported in other main microbes including *Salmonella (*Zou *et al*., 2012) and *P. aeruginosa* (Jakobsen *et al*., 2012) following exposure to plant-derived antimicrobials.

Because quorum sensing is a key process in social behavior and cell-to-cell communication in microbes, the findings could lead to the discovery of newdrug candidates that target vital physiological reactions/events in microbes. Despite having effective antibiofilm properties, the use of plant-derived antimicrobials has been hampered by a number of confounding factors, including difficulty in administration, the need for more contact time, and organoleptic considerations when used on food contact surfaces. As a result, several researchers have investigated the efficacy of new delivery methods including micellar encapsulation, biodegradable polymers, and polymeric films in enhancing plant compound antibiofilm action. Micellar encapsulated carvacrol, and eugenol, for example, were discovered to suppress and incapacitate *E. coli* O157:H7 and *L. monocytogenes* colony biofilms (P´erez-Conesa *et al*., 2006). Likewise, biofilm production was inhibited on polymeric films containing cinnamaldehyde and carvacrol (Nostro *et al*., 2012).

Nanoparticle-based drug delivery systems have received more attention in recent years as a means of improving drug antimicrobial efficacy (Singh & Lillard Jr, 2009). The primary benefits of nanoparticle-based drug delivery include sustained release, increased stability, and enhanced interaction of active ingredients with pathogens at the molecular level (Gelperina *et al*., 2005), which increases antimicrobial activity. Nanoparticles with phytochemicals like eugenol, trans-cinnamaldehyde (Gomes *et al*., 2011), and resveratrol (Sanna *et al*., 2012) or essential oils of Nigella sativa (Alhaj *et al*., 2010) and garlic (Yang *et al*., 2009) have recently been studied for their antimicrobial potential. The researchers discovered that nanoparticle preparations were steadier and more potent in mitigating the survival of some bacterial pathogens such as Listeria and Salmonella spp. Presently, research is being conducted to examine the efficacy of different nanoparticle-based delivery systems comprising plant-derived antimicrobials (Lannitelli *et al*., 2011) for removing biofilms from hospital devices (Tamilvanan *et al*., 2008) and food processing environments (Ferreira *et al*., 2010). Carvacrol-encapsulated poly (DL-lactide-co-glycolide) (PLGA) nanoparticles have been discovered to have mitigating effect on *Staphylococcus epidermidis* microbial biofilms (Lannitelli *et al*., 2011). Another study found that PLGA coatings containing cinnamaldehyde and carvacrol inhibited biofilms of *P. aeruginosa, S. aureus,* and *E. coli* (Zodrow *et al*., 2012).

IMPAIRED CELLULAR METABOLISM AND MEMBRANE DISRUPTION

Even though the precise mechanisms by which plant-derived antimicrobials exert antimicrobial action are unknown, different possible mechanisms have been documented which include bacterial cell membrane disruption, which results in membrane potential loss, impaired ATP production, and intracellular content leakage (Tsuchiya & Iinuma, 2000). Furthermore, metal ion chelation, altered membrane permeability and membrane-bound ATPase inhibition caused by plant-derived antimicrobials disturbusual bacterial physiological events and cause cell death (Burt, 2004; Gill & Holley, 2004). Plant-derived antimicrobials such as catechins, eugenol, thymol, andcarvacrol work by disrupting cell membranes, allowing cell contents to be released and ATP to be lost (Burt, 2004; Lambert *et al*., 2001). Cinnamaldehyde, on the other hand, has been shown to deplete intracellular ATP by inhibiting ATPase dependent energy metabolism as well as inhibiting glucose uptake and utilization (Oussalah *et al*., 2006; Gill & Holley, 2006). Exposure of bacteria to phenolic compounds has been demonstrated to induce cell wall lysis (Borneman *et al*., 1986).

CONCLUSION AND FUTURE PROSPECT

There is strong evidence that different variety of phytochemicals have the prospective of becoming effective antimicrobial medications that might be used to mitigate or treat microbial and viral infections. Although there are some promising *in vivo* effects in inhibiting pathogenic microbes without harming beneficial bacteria in the gastrointestinal tracts, more research on the safety and efficacy of these phytochemicals is needed to determine whether they could offer therapeutic benefits over current therapies. Furthermore, antimicrobial medications combined with phytochemicals may be more effective antibacterial agents than antimicrobial drugs alone. Due to the increased consumption of phytochemicals and other dietary phytochemical-rich supplements, it is necessary to determine whether using these formulations in conjunction with conventional medications can cause complications. Extensive investigations that can

determine the implications of phytochemical-drug interactions are limited. All of this evidence suggests, however, that while antimicrobial agents are applied to the body, phytochemical-rich foods should be considered in future research. Taken together, the prospect of utilizing phytochemicals as antimicrobial agents would demonstrate a major breakthrough in terms of prospective therapeutic benefits and safety in combating microbial resistance to drugs.

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Chapter 12
The Use of Plant Extracts as Potential Cancer Agents:
Approach to Plant-Derived Cancer Drugs

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ABSTRACT

The number of people with cancer and death rates are constantly increasing in the world. Although surgery, radiotherapy, and chemotherapy are still the most preferred methods, they have inadequacies, limited efficacy, and side effects. Therefore, development of new treatment methods has gained importance. Natural products were used for medical and therapeutic purposes in ancient times and are still used today. While some naturally derived molecules have already been shown to be effective against cancer, studies are ongoing for many natural molecules as cancer therapeutics. There are still many plant species and compounds whose effectiveness has not yet been discovered in the world. Therefore, identifying potential natural compounds that can be used in cancer treatment, demonstrating their effects on different types of cancer, and elucidating their mechanisms of action will lead to the discovery of new natural compound-derived drugs and overcome the existing difficulties of cancer.

INTRODUCTION

Cancer is known to be a global health problem responsible for the most deaths worldwide after cardiovascular diseases. While most human cancers are caused by exposure to a variety of environmental carcinogens, including chemicals, radiation, and viruses; and rearrangement of chromosomes, tumor suppressor genes, or spontaneous mutation also cause cancer (Reddy *et al.,* 2003). Stages of cancer progression are now defined as a long-term developmental process that is dynamic, multifactorial, and involving a range of signaling systems. From initiation and progression, the gradual development of cancer is followed by the progression stage and eventually results in metastasis, which leads to the uncontrolled spread of the cancer in the body (Aravindaram & Yang, 2010).

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Cancer and Current Treatment Approaches

According to GLOBOCAN 2020 data, an estimated cases of new cancer patient about 19.3 million and nearly 10 million deaths occurred globally (GLOBOCAN, 2020; Debela *et al.,* 2021). Moreover, In 2040, the worldwide cancer burden cases are anticipated to reach 28.4 million, an increase of 47% compared to 2020 (Sung *et al.,* 2021). For this reason, many studies are carried out for the treatment of cancer. Cancer treatment usually requires careful planning, therapeutic approaches, and guidelines. And also individual treatment options will be determined by a variety of parameters, including cancer type and stage, general health, other health problems, and personal preferences.

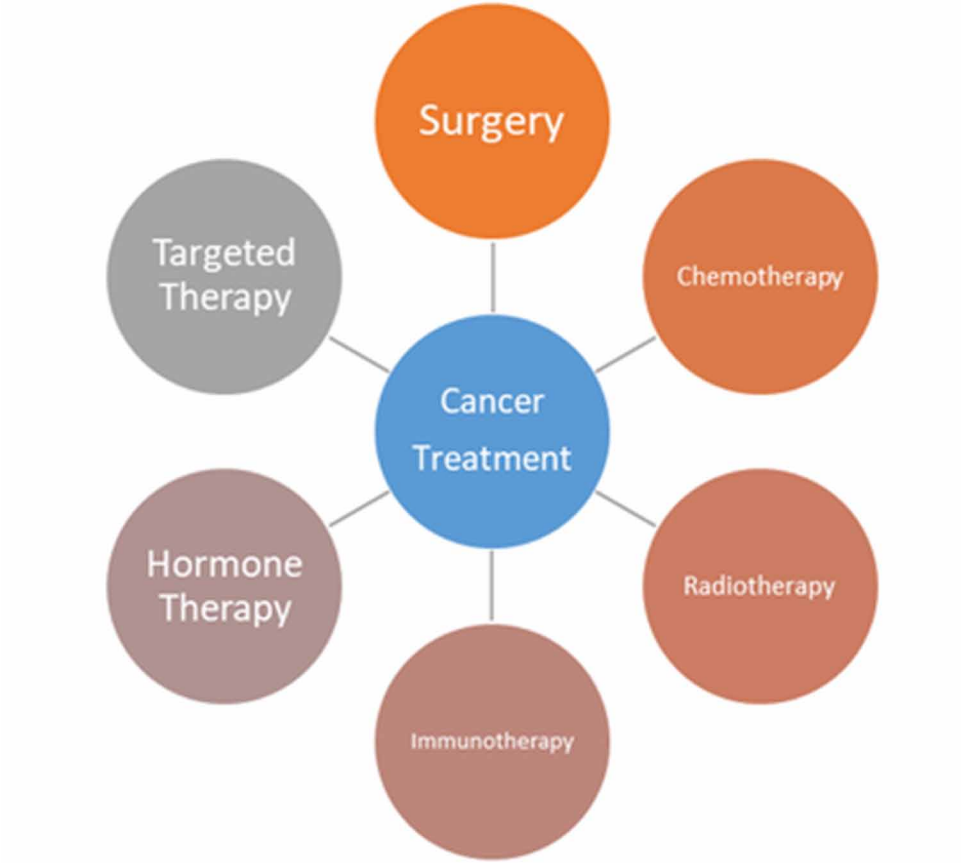
Methods such as surgery, radiotherapy and chemotherapy have been preferred for a long time (Hameed *et al.,* 2019, Shi *et al.,* 2022). These treatment methods can be applied as single treatment or in combination. In most cases, metastasis of cancer cells to adjacent and distant tissues and organs limits the effectiveness of surgery, and it is not possible to surgically remove all of the cancerous tissues and organs, especially in advanced stages (Ashrafizadeh *et al.,* 2021). However, current therapeutic approaches, including chemotherapy and radiotherapy, have high systemic toxicity, limiting their tolerability and clinical application, and are not effective in preventing advanced cancer cells (Ashrafizadeh *et al.,* 2021; Kashyap *et al.,* 2021). This treatment technique is related with severe side effects such as nausea and vomiting, diarrhea, anemia, loss of hair, soreness and exhaustion, which have an impact on people and their psychology. In addition, dose-dependent toxicity in healthy cells is one of the biggest obstacles in cancer treatment (Miao *et al.,* 2017). In order to eliminate these obstacles, new generation treatment methods such as immunotherapy, hormone therapy and targeted therapy are also applied (Figure 1) (Hameed *et al.,* 2019). Hence, it has become very important to find more effective and more selective treatment methods for the treatment of different human cancers. For this purpose, in studies conducted to discover new methods, it has been shown that structurally diverse compounds derived from various natural products can have chemopreventive effects against cancer as well as chemotherapeutic activities (Cragg & Pezzuto, 2016; Kashyap *et al.,* 2021).

HISTORY OF NATURAL PRODUCTS

Organic compounds are classified as either primary or secondary metabolites. Primary metabolites are essential for species growth and development, whereas secondary metabolites are considered to have a role in defense (Mosunova *et al.,* 2020). Secondary metabolites of species such as plants, animals, marine invertebrates, and bacteria are known as natural products and these natural products have historically played important roles in human health, mainly in ancient Asian and Middle Eastern cultures (Kittakoop, 2015). They evolve in nature in response to the natural environment's requirements and difficulties (Demain & Vaishnav, 2011). For centuries, humans have used naturally occurring substances for medicinal purposes, such as plants, which were first used as food, and as poisons over time, then their therapeutic properties were discovered and started to be used in the treatment of diseases. Ancient science anthologies have remained a vital source of modern pharmaceutical discovery in traditional and ethical medicine. They are still important fundamentals in pharmacy practice (Zhang *et al.,* 2020).

Before the 1800s, the active ingredients of most drugs, often plant-based and often used as extracts, oils, remedies, potions or mixtures, were unknown. The earliest records date back to 2600 BC. These records are written on clay tablets and come from the Cuneiform script in Mesopotamia era (Cragg &

Figure 1. Cancer Treatment Methods.



Newman, 2005a). Most of the 1000 or so plant-based drugs used at that time in these records are still used as treatments for inflammation, flu, cough, and parasite infestation (Gurib-Fakim, 2006). The "*Ebers Papyrus*" is the most well-known of these documents (Gurnani *et al.,* 2014). It is one of the oldest and most important ancient Egyptian manuscripts containing medical information. In this document, close to 1000 different substances and formulations have been documented, most of them are plant-based drugs (Nakanishi, 1999). The *Shennong Bencao Jing*, the oldest Chinese medical manual, was written in the 1st century AD. It lists 365 medicines, 252 of which are herbs. *Wu Shi Er Bing Fang* contained prescription lists for various diseases, exemplified by Recipes for Fifty-Two Diseases and it was revealed during the excavation of the Ma Wang Dui tomb at Changsha, China, in 1973. *Tang Herbal*, compiled in the 7th century (659 AD), is considered the first official Chinese pharmacopoeia to describe 850 medicines. Compared with *Shennong Herbal*, *Tang Herbal* records more medicine and more detailed; new uses and qualities of existing medicines are also explained, and the number of drugs in *Shennong Herbal* has more than doubled (Leung, 1990). Ayurveda in India emphasizes plant-based treatments. Indian materia medica contains information on storage methods and shelf life of harvested materials (Parker, 1915).

Plants represent the second largest source of biodiversity (Tan *et al.,* 2006). According to the World Health Organization (WHO), almost three-quarters of the global population use herbs and other forms of traditional medicine to treat diseases (Pandey & Madhuri, 2009). In addition, traditional medicines

have been passed down through generations as a result of acquired experience. Also, it has been reported that the use of herbs and herbal medicines has increased considerably in recent years, even in the United States (Rao *et al.,* 2004). Despite their popularity and essential role in the traditional and alternative medicine, very few terrestrial plants have been investigated for therapeutic potential (Tan *et al.,* 2006).

The use of therapeutics derived from plants continued in Greek and Roman cultures. Historians consider Theophrastus to be the Father of Botany as he authored a treatise called *Historia Plantarium* about 300 BC. This treatise contained plant organization and classification, plant information, and botanical morphology. The Greek physician Pedanius Dioscorides wrote a five-volume treatise on medical subjects entitled *De materia medica* which contains around 600 plants as well as medically beneficial animal and mineral products. In the Middle Ages, while Europe preserved the plant-based therapeutic knowledge of the West, the Arabs continued the Greco-Roman knowledge with their own culture. During this period, Avicenna wrote two very important books. One of them, *The Canon of Medicine*, has listed 800 simple medical substances (Cragg & Newman, 2005a).

Most recently, use of natural compounds first began in the early 19th century with the isolation of morphine from opium in 1806, which is considered a milestone, marked the beginning of the chemical primary stage of active ingredients from natural products (Klockgether-Radke, 2002; Clardy & Walsh, 2004; Balunas & Kinghorn, 2005; Ouyang *et al.,* 2014). The isolation of morphine has prompted the investigation of many other plant compounds such as quinine, caffeine, nicotine, atropine (Wang *et al.,* 2017; Bernardini *et al.,* 2018).

In the second half of the twentieth century, products of natural origin started to gain importance and the pharmaceutical industry gave priority to research and development for new products of natural products that can be used in the treatment of many diseases (Bernardini *et al.,* 2018). As a result, the great success of drug discovery programs derived from natural products led to obtain patents from the 1980s to the 1990s (Koehn & Carter 2005; Bernardini *et al.,* 2018). For this reason, even today, research on the discovery of products of natural products continues rapidly not only in the pharmaceutical industry, but also in academic and start-up project research.

MEDICINAL PLANTS AND NATURAL PRODUCTS AS A CANCER AGENTS

Nature is the source of research because it is home to millions of species of plants, animals, marine organisms, and microorganisms and development of new candidate therapeutic compounds, precursors for new drugs, and new chemical components as with many medicines made from these natural compounds (Newman & Cragg, 2016; Yin *et al.,* 2019). Natural products are widely recognized as the primary source of novel medicines and therapeutic agents and act as precursor molecules for the synthesis of various potent drugs. Drug discovery and development strategies from natural products differ at various stages. Plant activity information supplied the foundation for the enhancement of natural products. In ancient times, faced with the challenge of unknown diseases, natural products were discovered through mistakes and trials. Today, the therapeutic effects of natural compounds are discovered with the knowledge from the past and their active components are isolated (Zhang *et al.,* 2020). The reason why natural resources are so important is that they are used in the pharmaceutical industry and the pharmaceutical industry has very high values. The annual global pharmaceutical market is valued at approximately 1.27 trillion U.S. dollars by the end of 2020, and in 2021, this amount is thought to be around 1.5 trillion dollars. Approximately 35% of the drugs on the market are obtained directly or indirectly from natural products.

The vast majority of them are plants with a rate of 25% and followed by microorganisms (13%) and animals (about 3%) (Calixto, 2019). As a result, naturally derived products are an immensely valuable and advantageous resource for global pharmaceutical corporations developing novel drugs. Natural products are a resource for the development of semi-synthetic drugs, in addition to being a direct supply of drugs; can be used as prototypes for the development of precursor compounds or as taxonomic markers for the discovery of novel medications (Veeresham, 2012; Calixto, 2019). Natural products or their derivatives constitute approximately one-third of the best-selling drugs in the world. The FDA has approved a total of 1602 drugs by the end of September 2019. Though 286 of the approved drugs are derivatives of natural products, 8 of them are botanical drugs (Newman & Cragg, 2020).

Plant species protect themselves from potential predators and have the capacity to inhibit other competing plants to protect their territory have survived through natural selection (Mans *et al.,* 2000). As a result, secondary metabolite producers evolved in response to their local environment. If the metabolites were helpful to the producing species, the biosynthetic genes were maintained, and genetic alterations improved the process even more. Regarding biological activity, it has been stated that there are over 200,000 biological compounds that are active and/or toxic. (Demain & Vaishnav, 2011).

Natural products are composed of small molecules and have structural and chemical diversity. These have been evolved as drug-like compounds and continue to be the greatest drug sources and drug precursors (Newman & Cragg, 2012; Shen, 2015). Natural products play a very important role, especially in the discovery and development of anti-tumor drugs. The development of new plant-derived natural products and analogues for anticancer activity details efforts to synthesize novel derivatives based on the isolation and characterization mechanism for bioactivity and action combined with rational drug design-based modification (Pandey & Madhuri, 2009; Xu *et al.,* 2019). Currently, more than 60% of anti-tumor drugs are derived from natural sources such as plants and marine organisms, as simple synthetic modifications or as copies of naturally-derived substances and many are considered to have the ability to involve variety of cell death pathways including apoptosis and autophagy, or inhibiting cell proliferation in a variety of cancer cells (Newman *et al.,* 2003; Rosangkima & Prasad, 2004; Taylor, 2005; Pandey & Madhuri, 2009; Luqman & Pezzuto, 2010; Seelinger *et al.,* 2012). In addition to these, it is thought that there are many plants that have not been researched although they have anticancer potential (Ghagane *et al.,* 2017).

Discovery and understanding of cellular pathways is an important process of drug discovery processes. Natural products, as biochemical components that demonstrate the significance of certain pathways in disease and their potential in drug discovery, play an essential role as a source of innovation at this stage (Gullo *et al.,* 2006).

The discovery of the molecular pathways underlying cancer progression has resulted in the creation of various anticancer medicines. The main goal in cancer chemotherapy is to make selective drugs that will kill malignant tumor cells with high efficiency without harming healthy cells. However, many chemically synthesized anticancer drugs have caused significant harm to patients by suppressing the immune system (Rayan *et al.,* 2017). Therefore, there is a great need for the development of new chemopreventive agents that are both effective and safe and development of novel drugs based on natural products has been the focus of many researches (Sporn & Liby, 2005; Khazir *et al.,* 2014; Wright, 2017; Yao *et al.,* 2017). Their low toxicity and potential anticancer effects have been the reason for the investigation of natural products (Yin *et al.,* 2019). Alkaloids, flavonoids, terpenoids, polysaccharides, saponins, and other natural bioactive compounds with anticancer potential have been found (Avato *et al.,* 2017; Joshi *et al.,* 2017; Majumder *et al.,* 2017). Each natural product can work in different ways and interfere in different ways. They provide to influence a wide range of targets or sections of the signal transduction pathway

that regulate gene expression, cell cycle regulation, proliferation, cell death pathways, metabolism, and apoptosis. Various studies have reported that the anticancer activity of medicinal plants is due to the presence of antioxidants present in them. The low side effects of naturally occurring phytochemicals make them usually safe and well tolerated when compared to synthetic chemotherapeutic drugs, which is one reason for their popularity (Prema *et al.,* 2011;Sanmukhani *et al.,* 2014; Haroyan *et al.,* 2018; Kantartzis *et al.,* 2018; Ashrafizadeh *et al.,* 2021).

Aloe vera

Aloe vera has compounds that increase immune cells against cancerous cells. It has also been found that *Aloe vera* inhibits metastasis (Xu *et al.,* 2007). Expanded studies on this plant are ongoing.

Annona muricata

Graviola (*Annona muricata*) has acetogenin components which have anticancer effects via causing apoptosis and autophagy (Jacobo-Herrera, 2019). It has been shown to be efficient against various cancers, including breast cancer, liver cancer, prostate cancer, lung cancer, and colon cancer (Yajid *et al.,* 2018).

Brassinosteroids

Brassinosteroids are known as a class of polyhydroxylated steroid phytohormones in plants and naturally occuring compounds. Brassinosteroids regulate growth and differentiation of cells. By interacting with the cell cycle, it can induce responses required for growth inhibition as well as death (Malíková *et al.,* 2008).

Camptothecin

Camptothecin is an alkaloid originally isolated from the trunk tree of the *Camptotheca acuminata* (Nyssaceae) tree (Wall *et al.,* 1966; Tredwell & Gouverneur, 2012). Camptothecin shows anticancer activity by inhibiting the nuclear topoisomerase 1 enzyme which regulates DNA topology during cell replications (Merli, 2019). Also camptothecin induces apoptosis via double strand DNA damage (Verma & Hansch, 2009). Camptothecin has shown anticancer activity against many types of cancer, especially breast, ovarian and lung cancer (Wang *et al.,* 2019).

Curcuma longo L.

Curcumin is the active components of *Curcuma longo* also called turmeric. Although it is frequently used in South Asian and Middle Eastern dishes, it has an important place in Chinese medicine. The anticancer effect of curcumin has been demonstrated at all steps of cancer development (Zishan *et al.,* 2017) in addition, curcumin also shows protective effects against cancer formation (Liu & Ho, 2018). Curcumin exerts its anticancer activity by inducing apoptosis and suppressing various cellular signaling pathways and it is used to treat prostate cancer, colorectal cancer, head and neck squamous cell carcinoma, breast cancer and glioblastoma (Vallianou, 2015; Liu & Ho, 2018; Tomeh *et al.,* 2019).

Colchicum autumnale

Colchicine is a secondary metabolite isolated from the *Colchicum autumnale*. It is considered as a potent antimitotic drug that can be used both *in vitro* and *in vivo* because it causes mitotic arrest during the cell cycle as well as inducing apoptosis (Kumar *et al.,* 2017; Zishan *et al.,* 2017). Although it cannot be used clinically due to its toxicity, it is used as a precursor compound for the manufacture of potential anticancer drugs (Kumar *et al.,* 2017).

Camellia sinensis

Green Tea is obtained from the leaves of the *Camellia sinensis*. The feature that distinguishes green tea from black tea is that it is not oxidized and fermented (Ipek & Ergul, 2021). It predominantly contains epigallocatechin gallate, which protects against cancer by inhibiting carcinogens from covalently attaching to DNA (Zishan *et al.,* 2017; Chen *et al.,* 2020). Catechins show a synergistic effect when used in combination with other anticancer drugs (Yu *et al.,* 2014).

Etoposide and Tenoposide

Etoposide and tenoposide are podophyllotoxin compounds that are utilized in medicine. While podophyllotoxin inhibits mitosis by binding to tubulin, its semi-synthetic derivatives etoposide and teniposide form triple complexes with topoisomerase II and DNA, resulting in double-stranded DNA breaks and repair inhibition (Liu *et al.,* 1989; Chabner *et al.,* 2001; da Rocha *et al.,* 2001). They are used to treat a variety of malignancies, including leukemia, neuroblastoma, lung cancer, ovarian cancer, testicular cancer, and prostate cancer (Pelletier, 2003).

Flavopiridol

Flavopiridol is a semi-synthetic flavonoid derived from an Indian plant, rohitukine. Flavopiridol, a cyclin-linked kinase (CDK) inhibitor, has preferential activity especially against CDK9 (Kelland, 2000; Deep *et al.,* 2018) and also CDK1 and CDK2 (Kaur *et al.,* 1992). By interfering with the phosphorylation of cyclin-dependent kinases, flavopiridol arrests the cell cycle in the G1/S and G2/M boundaries (Senderowicz, 1999). In addition, Flavopiridol induces apoptosis (Tan *et al.,* 2002; Li *et al.,* 2017) and has antiangiogenic properties (Tan *et al.,* 2002; Senderowicz, 1999).

Ginkgo biloba

Ginkgo biloba seeds have been utilized in traditional Chinese medicine for centuries, while the leaf extracts are supplied as dietary supplements in many parts of the World (McKenna *et al.,* 2001; Mohanta *et al.,* 2014; Wang *et al.,* 2017). Ginkgo biloba extract contains a variety of bioactive components, including Ginkgolide-B (Feodorova *et al.,* 2020) and it may trigger apoptosis and inhibit the progression of human colon cancer, hepatocellular carcinoma, pancreatic and gastric cancer (Xu *et al.,* 2003; Chao *et al.,* 2004; Zhang *et al.,* 2008; Chen *et al.,* 2011; Zhao *et al.,* 2013).

Hypericum perforatum

Hypericum perforatum is also known as St. John's Wort. The active ingredient of this plant is hypericin and hyperforin. It inhibits tumor formation by inducing apoptosis (Schempp *et al.,* 2002).

Nigella sativa

Nigella sativa is a medicinal plant with a historical background and known as black seed. Many components were characterized in studies with the *Nigella sativa*, but the major ones were thymoquinone. Thymoquinone has been shown to suppress cell proliferation in breast, colon, ovary, lung, myeloblastic leukemia, and osteosarcoma cell lines (Shoieb *et al.,* 2003; Gali-Muhtasib *et al.,* 2004; El-Mahdy *et al.,* 2005; Rooney & Ryan, 2005; Roepke *et al.,* 2007; Wilson-Simpson *et al.,* 2007; Banarjee, 2010; Effenberger-Neidnicht & Schobert, 2011; Shankar & Srivastava, 2012).

Panax ginseng

Panax ginseng which is called Ginseng, has traditionally been used as a popular treatment for a range of diseases, including cancer, in several regions of the world. Ginseng contains ginsenosides, polysaccharides, flavonoids, volatile oils, amino acids, and vitamins as active components. Polysaccharides and ginsenosides probably responsible for the anticancer action (Nag *et al.,* 2012). It has been reported to play a role in apoptosis and cell cycle arrest (Chen *et al.,* 2014).

Quercetin

Quercetin is a bioflavonoid that is found in over twenty different plants including *Hypericum perforatum*. Quercetin has anticancer effects along with apoptosis, antiproliferative, growth factor suppression, and antioxidant activity (Lamson & Brignall, 2000; David *et al.,* 2016). It shows anticancer effect on breast, lung, kidney, prostate, pancreatic and ovarian cancer cell lines (Sharmila *et al.,* 2014; Lee *et al.,* 2015; Liu *et al.,* 2017; Baby *et al.,* 2018; Li *et al.,* 2018; Polukonova *et al.,* 2018; Vafadar *et al.,* 2020).

Taxol diterpenoids

Another of the plant derived cancer drug is taxol diterpenoids. Paclitaxel and docetaxel show impressive efficacy against many types of cancer. Paclitaxel enhances the polymerization of tubulin into stable microtubules and leading to mitotic arrest (Horwitz, 1994). Taxol derivatives used to treat a number of cancer types, including ovarian, esophageal, breast, lung, cervical and bladder cancer (Alqahtani *et al.,* 2019).

Vinca alkaloids

Vinca alkaloids (vinblastine, vincristine, and vindesine), epipodophyllotoxin lignans (etoposide and teniposide), taxane diterpenoids (paclitaxel and docetaxel), and camptothecin quinolone alkaloid derivatives (camptothecin and irinotecan) are the four primary structural families of plant-derived cancer treatments (Desai *et al.,* 2008; Pan *et al.,* 2010; Gurnani *et al.,* 2014). The discovery and development of the vinca alkaloids, vinblastine, vincristine, and vindesine, in the 1950s, triggered the search for

anti-cancer medicines derived from plants (Cragg & Newman, 2005b). Vinca alkaloids were the first to enter clinical application which are isolated from *Catharanthus roseus* (Madagascar periwinkle), which is used for the treatment of diabetes (Gueritte & Fahy, 2005; Cragg & Newman, 2005b). Its mechanism of action is to disrupt microtubules, causing cells to be arrested at metaphase and apoptotic cell death (Cragg & Pezzuto, 2016). Vinca alkaloids are the second most used class of cancer drugs and are used in the treatment of many types of cancer, including breast cancer, testicular cancer, leukemia, and lymphoma (Moudi *et al.,* 2013).

Viscum album

Mistletoe (*Viscum album*), another medicinal plant with anticancer activity, shows cytotoxic properties due to the plant lectins and other active substances (Zarkovic *et al.,* 2001*). Viscum album* extracts have anticancer activity against neuroblastoma (Esmaeili *et al.,* 2014), glioma (Kour *et al.,* 2014), ovarian cancer (Reynel *et al.,* 2018; Hwang *et al.,* 2019), cervical cancer (Hu *et al.,* 2011; Mavrikou *et al.,* 2020) and medullablastoma (Menke *et al.,* 2021).

Zingiber officinale

Zingiber officinale, known as ginger, has been used as a spice for centuries and has also been used medicinally for many years. It contains many active phenolic compounds. It has been shown to reduce cell growth by triggering G1 cell cycle arrest and apoptosis (Liu *et al.,* 2012).

Apart from these, plants such as *Punica granatum*, *Centaurea ainetensis*, *Cannabis sativa*, *Bolbostemma paniculatum*, *Lycopersicum esculentum*, *Solanum nigrum* L. have also been reported to have anticancer properties (Prakash *et al.,* 2013; Zishan *et al.,* 2017; Ipek & Ergul, 2021).

Apart from those mentioned above, there are compounds known to have cytotoxic effects on cancer. One of them, *Allium sativum*, has secondary metabolites such as alliin, alliinase, allicin, S-allyl cysteine, diallyldisulphide, diallyltrisulphide and methylallyltrisuphide (Divya *et al.,* 2017; Zishan *et al.,* 2017). It has been reported that *Allium sativum* has an anticancer effect against sarcoma, mammary carcinoma, hepatoma, colon cancer, and squamous cell carcinoma as well as its anti-metastasis effect (Lamm & Riggs, 2000; Zishan *et al.,* 2017).

THE FUTURE OF PLANT-BASED NATURAL COMPOUNDS AS DRUGS

Nature has been a significant source of novel drugs and drug precursors and new chemical formations since ancient times. The fact that 60-70% of the drugs on the market are directly or indirectly natural products proves this situation (Kumar & Jaitak, 2019). Natural product pharmaceutical discovery takes a significant amount of time and effort, starting from the collection of the plant and continuing with its authentication, isolation and targeted activity of new compounds.

Identification and specification of molecular targets associated with cancers form the basis of high-throughput anticancer drug discovery against targeted tumors. The pathways that promote apoptosis and the molecules found in these pathways are one of the most important of these targets (Özsoy *et al.,* 2020). Also cell death pathway that can be targeted is autophagy. Induction of molecules involved in autophagy may be beneficial in cancer prevention (Lan *et al.,* 2019). Another molecular target can be considered

as stopping the cycle by targeting cyclins and cyclin-dependent kinases, which have an important role in the cell cycle (Newman *et al.,* 2002). In addition, natural products play a cancer suppressing role in the epithelial-mesenchymal transition (EMT) (Lu *et al.,* 2020).

The obtained compounds do not always give the desired result and cannot be potential drug candidates. But as technology advances and new methods are found, drugs that failed in previous trials are being reconsidered. The ability to add drugs to carrier molecules in order to target certain tumors, which is one of these new methods, aims to demonstrate strong cytotoxicity against tumors while having no toxic side effects on healthy tissues (Cragg & Newman, 2005b). By transforming novel proteins that target and regulate various pathways in tumors into rapid and high-throughput candidates, plants will continue to be an important resource for new drug discoveries.

CONCLUSION

Medicinal plants have been used in the treatment of many diseases since ancient times. These treatment methods, which started as more primitive, have become more complex with the advancement of science. Identification and isolation of plant components has been very important both for drugs to be derived directly from plants and for their synthetic versions. These drugs are used in the treatment of many diseases and are very effective in treatments. Medicinal plants and their bioactive components, which have gained importance in the last few decades, are also frequently used in the treatment of cancer and successful results are obtained. Most importantly, whereas synthetic chemotherapy drugs destroy cells in a general manner, natural products have minimal toxicity to healthy cells. Considering that there are plants that have not been studied yet, bringing valuable information about them to the literature will be promising not only for cancer, but also for the treatment of many diseases that are quite common.

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Section 2

Biological Activities of Medicinal Plants and Natural Bioactive Compounds

Chapter 13
Beneficial Effects of *Moringa oleifera* Seed Oil Bioactive Compounds

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ABSTRACT

Humans have always been on the lookout for health-promoting drugs. Edible oils are one of the most well-known items for their nutritional and health benefits. This study looked at bioactive compounds in Moringa oleifera seed oil (MOSO) and its enormous potential use in the production of a variety of beneficial products. In fact, Moringa oleifera (MO) is cultivated for nutraceutical and medicinal utilities. Nevertheless, MOSO is now being researched for its possible application as a natural antioxidant for both edible and/or medicinal drugs. The effect of the different extraction techniques of seed oil and the origin of moringa seeds on the amount and quality of bioactive compounds were investigated in the present work. According to the findings, MOSO is a good source of nutrients and may be classified as a health-promoting product and can be used as a resource in the production of diverse culinary and medicinal items.

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INTRODUCTION

Medicinal plants have been employed for treating diseases in all cultures since ancient times (Malik *et al.,* 2005). Indeed, natural flora has become an extremely valuable source for health upgrading and treating several diseases across many human communities. Besides, a variety of plant species are still in use in many parts of the world such as Asia (Duraipandiyan *et al.,* 2006), South America (Bolzani *et al.,* 2012) and Africa (Khalid *et al.,* 2012) for remedies against several diseases. Despite the fact that the World Health Organization (WHO) have ascertained that the primary health care system for the 60% of the world's population, a large number of plant species with potential biological activities remain undiscovered (Li and Vederas, 2009). Traditional medicines' efficacy is now presumed due to its superior compatibility with human body, more cultural acceptance around the world and lesser adverse effects (Verma and Singh, 2008). More than 35,000 plant species are used for medicine in various human cultures around the world (Lewington, 1993) and for primary health care nearly 80% of the world populations rely on these traditional medicines which most of the time incorporate the use of seed oil and plant extracts most of the time (Sandhya *et al.,* 2006).

It is to be mentioned that ethnomedicinal studies play an important role in the discovery of novel drugs from homegrown medicinal plants and green pharmaceuticals are gaining popular approval due to their amazing properties (Yaseen *et al.,* 2015) because the unrivaled availability of chemical diversity and natural products, either as pure compounds or as homogenous plant extracts, provides vast opportunities for new drug discoveries (Jina and Sumitra, 2007). Herbal medicines, on the other hand, have no such side effects and due to the combinations of medicinal constituents coupled with minerals and vitamins have benefits over synthetic ones (Hussain, 2007).

In modern pharmacopeia about 25% drugs and also a great number of synthetic analogs prepared on Scientists' attention is currently being drawn to ethnomedicine as a result of the resuscitation of knowledge in traditional health practices across the world. As a result, the demand for herbal medicines and other natural products derived from various plant species has steadily increased in recent years. Since the history of ethnobotany, a lot of contemporary pharmaceuticals have been found, with a special emphasis on the documentation of traditional medicinal plant knowledge. 78 percent of novel chemical ingredients developed from medicinal plants are natural or natural product-derived compounds that are being employed as a possible alternative therapy for infectious disorders (Lokhande *et al.,* 2007). About 25% of medications and a large number of synthetic analogs based on proto-type chemicals derived from plants are found in current pharmacopeias (Mahmood *et al.,* 2013).

Moringa oleifera Lam. (MO) was widely utilized for its health advantages among plants recommended in traditional medicine. *Moringa oleifera* is a member of the Moringaceae family and is found mostly in India, as well as in other tropical and dry regions. MO is the most well-known Moringa variety because to its global distribution. Due to its beneficial characteristics and uses in the medical, food, and fuel sectors, all parts of the MO tree, including the seeds, leaves, roots, and even the flower, have been extensively researched. The seeds have drawn the interest of scientists because scientific interests as *M. oleifera* seed kernels contain a significant amount of oil (up to 40%) with a high-quality fatty acid composition. (oleic acid > 70%) (Abdulkarim *et al.,* 2005; Anwar & Rashid, 2007; Leone *et al.,* 2016; Bhutada *et al.,* 2016; Gharsallah *et al.,* 2021). *M. oleifera* seed oil (MOSO) contains approximately 98 percent fatty acids, 70 percent of which are unsaturated. The remaining 2% is made up of various hydrocarbons, fatty alcohols, carotenoids, pigments, tocopherols, tocotrienols, phytosterols, phenolic compounds, and small glyceridic chemicals (Andjelkovic *et al.,* 2010). M. oleifera seed oil (MOSO) (Andjelkovic *et al.,* 2010). Most of

these chemicals provide health advantages such as hypocholesterolemic effects (due to the presence of phytosterols) and free radical scavenging in the body (due to the presence of tocopherols, phenolics, and carotenoids), as well as a remarkable resistance to thermal and oxidative destruction. (Abdulkarim *et al.,* 2007; Gharsallah *et al.,* 2021).

The present chapter's major goal is to emphasize the health advantages of *Moringa oleifera* seed oil which has the potential to be employed as a natural and biological drug, by emphasizing its unique lipid profile and bioactive component content.

Moringa oleifera Seeds as Potential Source of Plant Oil

MO seeds have a high concentration of oil, ranging from 27.0 to 41.7 percent. Oil content variations might be attributable to plant species, growing regions, ripening phases, and extraction processes employed. In essence, the high rate of oil output recovered from *M. oleifera* seeds clearly demonstrate (Abdulkarim *et al.,* 2007; Gharsallah *et al.,* 2021).

Table 1. Oil Content in Moringa Oleifera seeds Cultivated Worldwide.

Seeds origin	Seed oil content* (%)	References
Tunisia	41.7 ± 3.71	Gharsallah *et al.,* (2021)
India variety Jaffna	39	Bhatnagar & Gopala Krishna (2013)
Kenya variety Mbololo	35.7	Tsaknis *et al.,* (1999)
Malysia	31	Mohammed *et al*., (2003)
Bangladeshi	37.5 - 40.2	Rahman *et al.*, (2009)
Algeria	27.0 - 37.4	Boukandoul *et al.*, (2017)
Brazil	39.0	Fernandes et *al.,* (2015)

*: content was calculated on a dry matter basis. The table shows the mean ± SD of three sets of analysis; SD: Standard Deviation.

Extraction and Processing of Moringa oleifera Seed Oil

It is widely proven that the level of oil yield extracted from MO seeds greatly depends on the procedure extraction. After mechanical pressing, the oil yield varied between 11% and 28.58% (Pereira *et al.,* 2016; Tsaknis *et al.,* 1998; Tsaknis *et al.,* 1999; Lalas and Tsaknis, 2002; Fakayode and Ajav, 2016). It is worth noting that the highest oil yield founded by Fakayode and Ajav (2016) was obtained by an optimization study in which *Moringa Oleifera* seeds were subjected to moisture content of 11% wet basis, and heated at 80 °C for 30 min at an applied pressure of 20 MPa. Duan *et al.* (2010) used ultrasonic assisted solvent extraction to obtain MOSO, and the optimal extraction rate was 36.3%, which was slightly lower than that observed by Chen *et al.* (2022) (38.61%) using CO_2 supercritical techniques as extraction procedure.

Yu (2009) reported that the latter oil yield level was even lower than those obtained by ultrasonic assisted, microwave-assisted, soxhlet apparatus, and water enzymatic extraction methods in which the yield was between 28 and 35.85%.

Fatty Acid Composition and High Nutritional Value Factors of Moringa oleifera Seed Oil

The fatty acid content of MOSO is shown in Table 26.2. Saturated fatty acid concentration ranging from 17.24 percent to 23.45 percent, in which palmitic acid dominates, followed by behenic, stearic, and arachidic acids. The oil is commercially known as "Ben" or "Behen" oil due to its high behenic acid concentration. *M. oleifera* seed oil contains trace amounts of cerotic, lignoceric, myristic, margaric, and caprylic acids. The oil includes a high percentage of monounsaturated fatty acids, up to 76 percent on average. Oleic acid is the most abundant fatty acid, accounting for between 70.2 and 77.40 percent of all fatty acids. Gadoleic and palmitoleic acids are two more monounsaturated fatty acids found in the oil. Some investigations have shown trace amounts of erucic acid (Lalas and Tsaknis, 2002). Polyunsaturated fatty acid concentration is quite low, averaging 1.50%, with linoleic and linolenic acid levels ranging from 0.40% to 1.27% and 0.17% to 1.39%, respectively. The extraction procedure appears to have no effect on the MOSO fatty acid composition. Nonetheless, fatty acid composition indicates that MOSO is high-oleic oil with a high monounsaturated to saturated fatty acid ratio (MUFA/SFA). The MUFA/SFA ratio is found in many oils, notably olive oil, and has been linked to a lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular stroke (Schwingshackl and Hoffmann, 2014). Hence, *M. oleifera* seed oil could be an acceptable substitute for olive oil as the main dietary fat in countries where the tree grows. *M. oleifera* seed oil has a monounsaturated fatty acid content comparable to that of olive oil (Boskou, 2011), but from a nutritional point of view, a lower content of polyunsaturated fatty acids is a limiting factor, which needs to be offset by the consumption of alternative sources rich in polyunsaturated fatty acids. Nonetheless, from a technological perspective, the low content of polyunsaturated fatty acids ensures greater resistance and stability to oxygen.

Minor Bioactive Lipids in *Moringa oleifera* Seed Oil as Nutraceuticals and Health Promoting Substances

Sterols

The sterol fractions of MOSO consist mainly of β-sitosterol, stigmasterol, campesterol and Δ5-avenasterol, accounting for 92% of the total sterols. Other phytosterols are present in trace amounts. It was reported that the composition of the sterol fraction is not affected by the extraction method. However, many factors could affect the total sterol content. In fact, Gharsallah *et al.* (2021) reported a total sterol content of 2896.2 ± 3.45 ppm on Tunisian cold pressed MOSO which was higher than that reported by Bhatnagar and Gopala Krishna (2013) (1700.8 ± 15.5 ppm) on MOSO originated from India and extracted by soxhlet using *n*-hexane as solvent. It is worth noting that cold-pressed extraction is without a doubt one of the processes that best adheres to the standards and would never jeopardize the quality of the extracted goods (Tsaknis *et al.,* 1999). Other factors, such as plant (type and cultivation agro-climatic conditions, may influence the sterol content of the oil (Anwar and Bhanger, 2003; Anwar and Rashid, 2007).

The sterol fraction is of interest due to its putative role in cholesterol metabolism and decreasing the circulating amount of low-density lipoprotein (LDL) cholesterol, also known as bad cholesterol (Abumweis *et al.,* 2008; Ras *et al.,* 2014). Gupta *et al.* (2011) speculate that β-sitosterol may have antidiabetic properties. However, dietary studies on the effect of plant sterols on cardiovascular risk remain contradictory and equivocal (Genser *et al.,* 2012).

Table 2. Fatty Acid Composition of Moringa Oleifera seed oil (%).

Fatty acids	Extraction technique				
	Cold pressing			Soxhlet extraction using *n*-Hexane	Cold extraction by Chloroform: Methanol (1:1)
	Pereira *et al.* (2016)	**Janaki (2015)**	**Gharsallah *et al.* (2021)**	**Anwar and Rashid (2007)**	**Variety ''Periyakulam 1'' Lalas and Tsaknis (2002)**
Caprylic acid (C8:0)	-	-	-	-	0.03
Myristic acid (C14:0)	0.2	-	-	-	0.13
Palmitic acid (C16:0)	5.80	12.97	6.11 ± 0.84	6.45 ± 0.20	6.36
Palmitoleic acid (C16:1)	1.4	-	1.4 ± 0.09	0.97 ± 0.07	1.49
Margaric acid (C17:0)	-	1.40	-	-	0.08
Stearic acid (C18:0)	6.20	2.95	5.37 ± 0.45	5.50 ± 0.25	5.74
Oleic acid (C18:1)	70.2	77.40	73.36 ± 0.22	73.22 ± 0.50	71.22
Linoleic acid (C18:2)	0.40	1.40	1.01 ± 0.06	1.27 ± 0.12	0.66
Linolenic acid (C18:3)	-	1.39	0.44 ± 0.22	0.30 ± 0.07	0.17
Arachidonic acid (C20:0)	3.70		3.26 ± 0.04	4.08 ± 0.10	3.60
Gadoleic acid (C20:1)	1.90		2.21 ± 0.25	1.68 ± 0.10	2.25
Behenic acid (C22:0)	5.6		5.71 ± 0.2	6.16 ± 0.15	6.28
Erucic acid (C22:1)	-		-	-	0.12
Lignoceric acid (C24:0)	-		0.66 ± 0.27	-	-
Cerotic acid (C26:0)	-		-	-	1.23
% Saturated fatty acids (SAFA)	21.50	17.24	21.11 ± 0.65	22.19 ± 0.55	23.45
% Monounsaturated fatty acid (MUFA)	78.10	80.70	76.97 ± 0.19	75.87 ± 0.67	75.08
% Polyunsaturated fatty acids (PUFA)	0.40	02.79	1.45 ± 0.16	1.57 ± 0.19	1.47

SAFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty Acids. Values are means ± SD of three determinations; SD: standard deviation.

Tocopherols and tocotrienols (tocochromanols)

M. oleifera seed oil has a high tocopherol concentration, which include α-, γ- and δ-tocopherols (Table 26.4). The amount of tocopherol in the oil may vary depending on the extraction process utilized. Indeed, Lalas and Tsaknis (2002) demonstrated that the concentration of α- and δ-tocopherol in oil obtained by cold pressing is much greater than that obtained by *n*-hexane and chloroform:methanol (1:1). Nonetheless, the tocopherol concentration of cold pressed MOSO is larger than that of oils produced using

Table 3. Sterol composition (%) of Moringa oleifera seed oil.

	Extraction techniques		
Sterols	**Cold pressing Gharsallah *et al.* (2021)**	**Soxhlet extraction using *n*-hexane Anwar and Rashid (2007)**	**Cold extraction by Chloroform: Methanol (1:1) Lalas and Tsaknis (2002)**
Cholesterol	0.19	0.99 ± 0.11	0.12
Brassicasterol	-	-	0.05
24-methylenecholesterol	0.17	-	0.09
Campesterol	13.87	17.95 ± 0.50	14.60
Campestanol	0.36	0.53 ± 0.10	0.33
Δ 7-Campestanol	-	0.70 ± 0.07	-
Stigmasterol	19.42	18.80 ± 0.50	22.50
Ergostadienol	-	-	0.36
Clerosterol	0.87	1.70 ± 0.10	1.80
β-sitosterol	47.24	46.16 ± 0.40	44.05
Stigmastanol	-	0.53 ± 0.05	0.74
Sitostanol	0.75	-	
Δ 5-avenasterol	10.57	9.26 ± 0.15	10.43
Δ 7-avenasterol	2.43	0.84 ± 0.10	1.15
Δ 5,23-stigmastadienol	0.87	-	-
Δ 5,24-stigmastadienol	1.33	-	
Δ 7,14-stigmastadienol	-	-	0.40
Δ 7,14-stigmastanol	-	0.76 ± 0.12	0.51
28-isoavenasterol	-	1.04 ± 0.11	0.40
Δ7-stigmastanol	1.89	-	-

Values are means ± SD of three determinations; SD: standard deviation.

other techniques. The concentration of α-tocopherol content, which has the highest vitamin E efficacy, is 101.11 ± 0.27 mg/kg. With such a high tocopherol concentration, MOSO should be predicted to have strong oxidative stability and protection throughout storage and processing.

Total phenolic content (TPC) and phenolic compounds

Phenolics are naturally occurring lipid-soluble antioxidants, and the positive benefits of oils have been generally linked to their phenol concentration (Quideau *et al.,* 2011). Tocopherols and tocotrienols, flavonoids, sterols, and phenolic acids are among the bioactive oil components (as esterified or free molecules, aldehyde forms, and glycosides). Except for sterols that have beneficial effect on serum lipids (decreasing LDL-C and increasing HDL-C), the other compounds have primarily radical scavenging, antioxidant and anti-inflammatory activities (Pandey and Rizvi, 2009), and the ability to modulate the immune response, affecting the multiplication of white blood cells and the production of cytokines.

Table 4. Tocopherol (mg/Kg) composition of M. oleifera seed oil.

	Extraction techniques				
	Cold pressing			Soxhlet extraction using *n*-hexane Bhatnagar and Gopala Krishna (2013)	Cold extraction by Chloroform: Methanol (1:1) Lalas and Tsaknis (2002)
Tocopherols	Gharsallah *et al.* (2021)	Lalas and Tsaknis (2002)	Janaki (2015)		
α-tocopherol	101.11 ± 0.27	5.06	5.05	56.2 ± 1.6	2.42 ± 0.37
γ-tocopherol	86.87 ± 0.15	25.40	25.40	12.6 ± 0.8	5.52 ± 0.69
δ -tocopherol	10.36 ± 0.46	3.55	3.55	19.2 ± 0.6	12.67 ± 0.55
Total tocopherols	198.34 ± 0.88	34.01	34.00	88.0 ± 3.0	20.61 ± 1.61

Values are means ± SD of three determinations; SD: standard deviation.

Gharsallah *et al.* (2021) reported a TPC in Tunisian MOSO of 102 ± 2.41 mg Gallic Acid Equivalent (GAE) per Kg, such a result was similar to that found by Bhatnagar and Gopala Krishna (2013) in Indian MOSO Jaffna variety (118.9 ± 0.9 ppm) obtained with soxhlet apparatus using hexane as solvent. According to Nadeem and Imran (2016), MOSO exhibited a higher TPC (7.1 g GAE /100g) when compared to other vegetable oils and extracts. In fact, these authors found a TPC of 4.25, 6.45, 5.6 and 5.19 g GAE /100g, respectively in chia oil, Tamarind oil, and chia seed and date fruit extracts.

To our knowledge, there is relatively little data on the identification and measurement of phenolic chemicals in MOSO. Gharsallah *et al.* (2021) and Bhatnagar and Gopala Krishna (2013) discovered six phenolic compounds with a slight difference in composition in cold pressed and n-hexane MOSO. In fact, Gharsallah *et al.* (2021) noticed the presence of four phenolic acids (gallic, caffeic, vanillic, and ferulic), and two flavonoids (apigenin and naringenin). However, Bhatnagar and Gopala Krishna (2013) identified five phenolic acids (gallic, caffeic, vanillic, ferulic and cinnamic) and one flavonoid (vanillin).

Biological activities of *Moringa oleifera* seed oil

Antioxidant Activities

Several studies have found that *M. oleifera* seeds contain edible oil rich in natural antioxidants. According to Bhatnagar and Gopala Krishna (2013) and Chen *et al.* (2022), the MOSO concentration that inhibited 50% of free radicals (IC_{50}) using the DPPH assay was 35.5 mg/mL in Indian *M. oleifera* Jaffna variety seed oil extracted by soxhlet using n-hexane as solvent and 22.94 mg/mL in Chinese MOSO extracted under supercritical CO_2. On the other hand, according to Gharsallah *et al.* (2021) and Ogbunugafor *et al.* (2011) IC_{50} was 62 µg/mL in Tunisian cold pressed MOSO and 39.95 µg/mL in Nigerian MOSO extracted by soxhlet apparatus using *n*-hexane as solvent, respectively.

Bhatnagar and Gopala Krishna (2013) reported that MOSO is vastly rich in monounsaturated oleic acid (70.2-77.40%) and very poor in PUFA (0.40-2.79%). Besides, it contains an excess of antiradical molecules such as tocopherols, phenolics and carotenoids which prevent the peroxidation of PUFA and quench free radicals in the human body. Such a finding was consolidated by Gornas *et al.* (2015) who

Table 5. Phenolic compounds (mg/Kg) of M. oleifera seed oil.

Phenolic compounds	Gharsallah *et al.* (2021)	Bhatnagar and Gopala Krishna (2013)
Phenolic acids		
Gallic acid	0.20 ± 0.05	48.5 ± 1.2
Caffeic acid	4.30 ± 0.18	15.6 ± 0.7
Vanillic acid	0.20 ± 0.08	12.4 ± 0.3
Ferulic acid	22.90 ± 0.32	13.1 ± 0.5
Cinnamic acid		16.8 ± 0.8
Flavonoids		
Apigenin	16.12 ± 0.23	
Naringenin	20.70 ± 0.25	
Vanillin		11.5 ± 0.4

reported a clear correlation (r = 0.994) between the total tocochromanol (tocopherols and tocotrienols) contents in the oils and the DPPH radical scavenging activity.

Ojiako and Okeke (2013) suggest that the strong antioxidant activity of MOSO makes it a potential candidate in the field of natural anticancer drugs. That pointed out that antioxidants are believed to play an important role in the body since they are known not only to decrease serum low-density lipoprotein (LDL) levels, but also to prevent LDL oxidation. The authors conclude that MOSO is a good antioxidant and can be used as a cure.

Anti-inflammatory Activities

MOSO contains zeatin, a potentially bioactive substance which is believed to have antioxidant and anti-inflammatory properties when consumed or applied topically. It also contains β-sitosterol, which blocks the biochemical events of cholesterol formation and a high amount of oleic acid, both endowed with an anti-inflammatory characteristic. The richness of MOSO in these bioactive compounds makes *Moringa* oil beneficial for acne outbreaks (Nedeem and Imran, 2016). To the best of our knowledge, research information on MOSO's anti-inflammatory properties is limited.

Therapeutic Effects of Bioactive Compounds in *Moringa oleifera* Seed Oil

Therapeutic Effects of Oleic Acid

Owing to its advantageous effects on lowering low and high-density lipoprotein cholesterol in blood, the presence of a high concentration of oleic acid, the major monounsaturated fatty acid (MUFA) of MOSO, might be helpful in reducing cardiovascular disease. It is worth mentioning that, the high concentration of oleic acid in the membrane phospholipids makes the cell less prone to oxidation by limiting the formation of pro-inflammatory molecules. These chemoprotective characteristics are likely to translate into a variety of favorable health effects, including cardiovascular protection as well as, protection against viral infection and cancer development (Pauwels, 2011). Saturated fatty acid and linolenic acid reduc-

tions were observed to lower blood pressure, triglyceride levels, and platelet aggregation. (Wijendran and Hayes, 2004; Sánchez-Machado *et al.,* 2015).

The ability of oleic acid to reduce cardiovascular risks may be associated with an enhancement of serum lipoprotein profile (HDL-to-LDL) in patients with hypercholesterolemia (Zambon *et al.,* 2000; Bemelmans *et al.,* 2002), as well as improved endothelial function due to a rise in flow-associated vasodilatation in hypercholesterolemic patients (Fuentes et al., 2001) and a diminution in inflammation and oxidative stress (Chrysohoou et al., 2004). Moreover, there is a decrease in the use of antihypertensive medicines and the prevalence of degenerative illnesses, as well as improved blood pressure regulation in both people and animals. (Psaltopoulou *et al.,* 2004; Visioli *et al.,* 2005; de Lorgeril & Salen, 2006; Carrilo *et al.,* 2011) and rats fed a diet rich in oleic acid (Herrera *et al.,* 2001; Alemany *et al.,* 2004).

According to Yang *et al.* (2005) and Funari *et al.* (2003), adrenergic and receptors are important in modulating central and peripheral blood pressure and these pathways can be modulated by oleic acid due to its effects on cell membrane structures. This monounsaturated fatty acid may act through modulating membrane lipid structures and cell signaling platforms, as well as by regulating the adrenergic receptor pathways that involve G protein dependent signaling and results in blood pressure control (Yang *et al.,* 2005). Indeed, increased levels of MUFA on cell membrane can alter the localization, activity and the expression of other key signaling molecules increasing the production of vasodilator stimuli (cAMP and PKA) and decreasing the action of vasoconstrictor pathways (inositol-triphosphate, Ca^{+2}, diacylglycerol and Rho kinases) (Alemany *et al.,* 2006). Teres *et al.* (2008) revealed *in vivo* that the high oleic acid concentration in olive oil, rather than its minor components, is responsible for the normotensive effects attributed to olive oil intake, both in chronic and acute experimental treatments employing oleic acid. In terms of MOSO's anticancer effects, Abd-Rabou *et al.* (2016) found the nano-form of the oil had a stronger impact on the colorectal cancer Caco-2 and HCT cytotoxicity via mitochondrial malfunction triggering. According to Sales-Campos *et al.* (2013), high oleic acid consumption is already associated with a lower risk of cancer development (primarily breast, colorectal and prostate cancer), whereas diets high in total fat and linoleic acid or saturated fatty acid are associated with an increased cancer risk. (Binukumar & Mathew, 2005).

Llor and Plons (2003) conducted *in vitro* tests to assess the effect to evaluate the effect of oleic acid on colorectal cancer cells and discovered that it caused apoptosis, cell differentiation and down regulated the expression of COX-2 and Bcl-2, which are associated with inflammation and apoptosis. In this work, although it was not proved that oleic acid had direct effects on COX-2 or Bcl-2 in this study, the authors showed a specific induction of apoptosis in HT-29 cells. Oleic acid intake has also been shown to impact the beginning, development, and advancement of carcinogenesis with tumors achieving a reduced degree of clinical and histological malignancy in these situations (Costa *et al.,* 2004; Escrich *et al.,* 2006).

In line with this, oleic acid has been shown to serve a crucial chemoprotective effect in breast cancer cell lines. In vitro treatment of breast cancer cells with oleic acid suppressed the oncogene Her-2/neu expression that is overexpressed in roughly 20% of breast carcinomas and encode the oncoprotein Her-2/neu which controls, in normal cellular conditions, many cell functions such as cell differentiation, proliferation and apoptosis. A disruption in the expression of this protein increases the risk of cancer development. Furthermore, the capacity of oleic acid to function synergistically with the monoclonal antibody trastuzumab, which is employed as a cancer treatment by targeting Her-2/neu, has already been documented (Menendez *et al.,* 2005).

Therapeutic effects of β-sitosterol

MOSO's main phytosterol is β-sitosterol. It has been shown in many *in-vitro* and *in-vivo* studies that β-sitosterol has a various biological actions, including anxiolytic and sedative effects, analgesic, immunomodulatory, antimicrobial, anticancer, anti–inflammatory, lipid lowering effect, hepatoprotective, protective effect against respiratory diseases, antioxidant and anti-diabetic activities. (Babu & Jayaraman, 2020). According to a recent study, β-sitosterol prevents the high-fructose diet-inducing hypertriglyceridemia, visceral obesity and hypoadiponectinemia (Gumede *et al.,* 2019). It also boosts glycemic control and diminishes insulin resistance through the regulation of IRS-1/Akt mediated insulin signaling in adipose tissue of high fat diet and sucrose induced type-2 diabetic rats.

Oxidative stress plays an important role in the genesis and progression of various illnesses, including atherosclerosis, liver cirrhosis, cardiovascular diseases, cancer and diabetes. Persistent hyperglycemia in diabetes increases the generation of free radicals, can initiate lipid peroxidation, which results in the stimulation of non-enzymatic glycation of protein, variations in structure and function of basement membrane and collagen and enzyme inactivation, all of which contribute to the development of diabetes complications (Liguori *et al.,* 2018; Oguntibeju, 2019). Because oxidative stress is a key contributor to the development of diabetes mellitus, antioxidants are thought to be useful therapy alternatives.

Numerous scientific investigations indicate that β-sitosterol has antioxidant properties that operate chemically as a minor radical scavenger and physically as membrane stabilizers (Yoshida & Niki, 2003; Gupta *et al.,* 2011). It has been substantiated that, β-sitosterol reduces oxygen free radicals and hydrogen peroxide levels in Phorbolmyristate acetate (PMA) stimulated RAW 264.7 cells and increases the enzymatic antioxidant which is manifested by the activation of estrogen receptor/PI3-kinase-dependent pathway. It also reverses the impairment in glutathione/oxidized glutathione ratio which proposed that the phytosterol could be a possible reactive oxygen species (ROS) scavenger, indicating that phytosterol might be a potential reactive oxygen species (ROS) scavenger (Vivancos and Moreno, 2005). Another study conducted by Baskar *et al.* (2012) corroborates earlier scientific findings in which the authors revealed that β-sitosterol treatment improves enzymatic and non-enzymatic antioxidant in 1,2-dimethylhydrazine-induced colon carcinogenic rats and this study demonstrated that β-sitosterol may be recognized as a potential chemopreventive drug for colon cancer.

Babu & Jayaraman (2020) reported that administering β-sitosterol (20 mg/kg body weight, orally for 30 days) to high fat diet and sucrose-induced type-2 diabetic rats, corrected the transformed levels of blood glucose and serum insulin. It also brought the lipid profile, oxidative stress indicators, and antioxidant enzymes back to near-normal levels. They also discovered a substantial drop in insulin receptor and glucose transporter 4 (GLUT4) proteins as a result of high fat diet, emanating from insulin resistance that results in reduced glucose oxidation and uptake in type-2 diabetic rats.

Effects of Phenolic Compounds

Phenolics provide important roles in the reproduction and development of the plants, act as defensive mechanisms against pathogens, parasites, predators, and UV irradiation. They also contribute to plant color. Aside from their activities in plants, phenolic compounds in our diet may give additional health benefits such as a lower chance of acquiring chronic illnesses (Liu, 2013).

Cardio-protective Activity

Atherosclerosis is a chronic inflammatory disease characterized by accumulation of leukocytes in the vascular wall. Platelets coaggregate with leukocytes via P-selectin glycoprotein ligand-1 (PSGL-1) and P-selectin contacts and play an important role in the development of atherosclerotic plaques and thrombosis (Davi and Patrono, 2007; Aukrust *et al.,* 2010). Gallic acid has been discovered to have anti-atherosclerotic activity by limiting platelet activation and its association with leukocytes which is likely to be through decreasing intracellular Ca^{2+} mobilization via regulating the signals of PKCα/p38MAPK and Akt/GSK3β (Chang *et al.,* 2012). It has been found that ferulic acid substantially inhibited copper ion-induced LDL oxidation and promoted cholesterol absorption and breakdown in the liver (Zang *et al.,* 2000). Park *et al.* (2011) found that phenolic acids decreased oxidized LDL absorption in murine macrophages by downregulating membrane expression of SR-B1, a membrane receptor on macrophages that is responsible for the internalization of oxidized LDL and causes cellular cholesterol buildup (Yue *et al.,* 2010). Likewise, phenolics acids also increase cholesterol efflux in lipid-loaded macrophages by promoting membrane receptor ABCA1 expression. ABCA1 is a membrane transporter prevalent in macrophages that plays an important role in cholesterol homeostasis, hence guarding against atherosclerosis (Xu *et al.,* 2009). The most prevalent cardiovascular condition is hypertension, which is mostly caused by lifestyle and food factors (Kumar *et al.,* 2014). Nitric oxide (NO) is important in the physiologic regulation of blood pressure and myocardial damage. Alterations in NO synthesis or bioavailability can produce vasoconstriction and might be involved in the pathogenesis of hypertension. Vanillic acid has been shown to reduce against cardiovascular complications aroused due to hypertension (Opie *et al.,* 2006). Vanillic acid hypertension and left ventricular function in hypertensive rat models produced by Nω-nitro-L-arginine methyl ester (L-NAME) induced hypertensive rat models. L-NAME inhibits NO synthase activity, resulting in hypertension and arteriosclerosis (Souza *et al.,* 2001; Pechànovà *et al.,* 2004; Mishra and Vinayak, 2011). Vanillic acid has cardioprotective effect, as evidenced by decreased cardiac marker enzymes (CK, CK-MB, and LDH), left ventricular functions, improved tissue nitric oxide metabolite levels, and upregulated mRNA expression of eNOS in L-NAME induced hypertensive rat.

Phenolic Acids in Cancer Cure and Treatment

Cancer is one of the world's biggest health issues, and according to a World Health Organization (WHO) report, cancer kills about twice as many people each year as AIDS, malaria, and TB combined (Reddy *et al.,* 2003). Epidemiology research suggests that a diet high in antioxidant-rich fruits and vegetables decreases the risk of various cancers, implying that particular dietary antioxidants might be useful agents for cancer incidence and mortality prevention. Phenolic acids and their derivatives, such as hydroxybenzoic and hydroxycinnamic acids, play an important role in cancer prevention and therapy. (Huang and Zhang, 2010; Kumar *et al.,* 2019; Badhani, 2015; Rocha *et al.,* 2012; Kumar *et al.,* 2016; Kumar *et al.,* 2017; Kumar and Goel, 2019). Plant phenolics may provide a chance in this area, and between the 1940s and 2006, more than half of all anticancer prescription medications authorized globally were natural compounds or their derivatives, with several clinical trials ongoing (Efferth *et al.,* 2007). In fact, phenolic acids reduce tumor initiation through several mechanisms, including preventing the formation of genotoxic molecules and inhibiting the activity of mutagen-transforming enzymes (Frassinetti *et al.,* 2012; Sloczynska *et al.,* 2014); regulating heme-containing phase I enzymes (Rodeiro *et al.,* 2009; Basheer and Kerem, 2015), carcinogen-detoxifying phase II enzymes (Munday and Munday, 2004; Kou et

al., 2013), and also stop the DNA adducts formation (Lu et al., 2008). The majority of phenolics work at various stages to treat or inhibit the various diseases (Choi *et al.,* 2014).

Phenolic Acids as Antidiabetic Agent

Diabetes has been recognized as an oxidative stress condition, the result of an imbalance between the generation of free radicals and the ability of the individual to oxidize them. Oxidative stress is widely connected with organ damage caused by reactive oxygen species (ROS) that are inadequately neutralized by antioxidants, resulting in inflammation and a range of metabolic diseases (Furukawa *et al.,* 2004). Antioxidants reduce free radical activity through a variety of methods, and phenolic substances, particularly phenolic acids (which have a high antioxidant and free radical scavenging capacity), operate against oxidative stress and associated obstacles by blocking the ROS generating enzymes. The phenolic acids have an effect on the function of the glucose and insulin receptors (have a crucial role in diabetes). Through PI3K/Akt activated protein kinase pathways, they increase the expression of glucose transporter 2 (GLUT2) in pancreatic β-cells (which create insulin) and boost the translocation of glucose transporter 4 (GLUT4). Chlorogenic and ferulic acids both stimulate transporters and act as anti-diabetic drugs (Jung *et al.,* 2007; Prasad *et al.,* 2010; Choi *et al.,* 2011; Ong and Hsu, 2013; Cherng *et al.,* 2013; Gandhi *et al.,* 2014). The best phenolic acid property is the inhibition of α-glucosidase and α-amylase (two important enzymes responsible for the conversion of dietary carbohydrates into glucose) (Hanhineva *et al.,* 2010).

Therapy of Skin Disorders

Plant phenolics, whether gained through food or skin application, may assist individuals by alleviating symptoms and inhibiting the development of certain skin problems, according to research (Dzialo *et al.,* 2016). Polyphenols' most prevalent properties—antioxidant, anti-inflammatory, and antimicrobial—indicate that they deserve to be recognized in natural medicine and may be extremely beneficial in the treatment of many skin issues. These three features are the major possible modes of action against diverse skin conditions. The antioxidant activity of phenolic compounds is linked to molecule's annular structure, conjugated double bonds and the presence of functional groups in the ring. The antioxidant activity of phenolics is achieved through a variety of mechanisms of action, including the inhibition of ROS formation, ROS trapping, and the extinction of singlet oxygen, as well as the reduction of chelated metal ions (which are catalysts for reactions leading to the formation of ROS), interrupting the cascade of free radical reactions in lipid peroxidation, and protecting other antioxidant-active compounds. (Samoylenko *et al.,* 2013; Liaudanskas *et al.,* 2014; Alov *et al.,* 2015; Andjelkovic *et al.,* 2006). Skin is well equipped with two crucial means of defense against oxidative stress: antioxidant enzymes (catalase, glutathione peroxidase and peroxide dismutase) and non-enzymatic molecules (vitamins, ubiquinone, glutathione) (Dudonne *et al.,* 2011). Nevertheless, the endogenous defense system against ROS is frequently inadequate. Thus, it is recommended to increase the amount of natural antioxidants through the diet or external application. Polyphenols have critical roles in the regulation of pro-inflammatory mediators, the neutralization of free radicals, reactive oxygen species (ROS), reactive nitrogen species (RNS), and hence the prevention of lipid peroxidation (Rhein *et al.,* 2010). Phenolic compounds also have significant antifungal, antiviral, and antibacterial properties (Czemplik *et al.,* 2011). Many types of infections or diseases, including the dermal kind, are treated with a broad activity spectrum antibiotic. A broad activity spectrum antibiotic is used to treat a wide range of infections and illnesses, including

cutaneous infections. It may have a detrimental impact on the skin's natural microflora and lead to resistance in many bacterial strains (Pinho *et al.,* 2014). More than 90% of staphylococci, pneumococci and enterococci isolated from serious infections have been found to be resistant to antibiotics; thus, the demand for antibacterial products is still rising. These medications can be used to treat multi strain bacterial infections without creating a detrimental effect on human tissues at the same time (Czemplik *et al.,* 2011). The mechanism of action of phenolics on cell membranes may explain their antibacterial characteristics (Wu *et al.,* 2013).

The epidermal skin cells have the ability to self-renew and replace dead cells indefinitely. The human epidermal turnover period is believed to be between 40 and 56 days. Unfortunately, the ability to regenerate cells declines significantly with age (Koster, 2009). Some physiologically active substances, such as phenolic chemicals, can, however, impede or even reverse this process. Dzialo *et al.* (2016) investigated phenolic compounds' possible anti-aging efficacy by examining their transcriptional effects on genes involved in oxidative stress protection, cell renewal, and inflammatory response pathways. Only the gene associated with inflammatory processes exhibited a reduction among the genes studied, which is consistent with the stimulating and protecting effects of phenolics. More crucially, skin renewal genes involved in proliferation, differentiation, survival, and DNA synthesis (which are known to be downregulated in normal NHDF cells) were upregulated about 2-fold; hence, they demonstrated effective gene transcription modulation (Dudonne *et al.,* 2011).

PERSONAL CARE FORMULATIONS

MOSO oil's high antioxidant activity may be used to create body creams with higher antioxidant activity, antibacterial and antifungal activity, and superior free radical inhibition (Ojiako and Okeke, 2013). The phenolic chemicals found in MOSO, on the other hand, may participate in the anti-inflammatory cascade through their antioxidant activity. This connection is mostly associated with their capacity to scavenge free radicals, hence reducing cellular harm (Biesalski, 2007). MOSO also provides softness and smoothness to dry and rough skin. The efficacy of lovastatin and *Moringa oleifera* were compared, and a rabbit research trial was done. The feed was supplemented with 6 mg/kg and 200 mg/kg every day. After 120 days of testing, both MOSO and lovastatin were shown to lower blood cholesterol, phospholipids, triglycerides, VLDL (very low-density lipoproteins), and LDL cholesterol. *Moringa oleifera* supplemented diets resulted in decreased fat in the liver, heart, and aorta of rabbits. Faecal examination demonstrated that cholesterol concentrations were greater in Moringa supplemented diet cases than in the control group (which did not get Moringa supplemented diet) (Mehta *et al.,* 2003).

Unlike other vegetable oils, MOSO was reported to be endowed with antiseptic effects, and to possess anti-rash characteristics. It also fights black heads, improves the strength of hairs, acts as anti-dandruff and prevents split ends. It is important to mention that MOSO a rich source of vitamin C prevents scurvy, guards bones, and calms the nervous system (Monica, 2005).

CONCLUSION

Due to the composition of lipid-soluble bioactives, interesting evidence on their impact to human health has been published. Indeed, the fatty acid profile (particularly omega-9) and high-value minor lipid com-

ponents (i.e., tocols, sterols, glycolipids, phospholipids, aroma compounds, and phenolics) demonstrate health-promoting properties and positively affect our body's biological activities. *Moringa oleifera* seeds have been described as an unconventional oil source rich in bioactive and nutraceutical components such as linoleic acid, carotenoids, tocopherols, tocotrienols, sterols, and phenolic compounds. Such phytochemicals are endowed with diverse biological activities mainly antioxidant, anti-inflammatory and antimicrobial properties and possess several health benefits, such anti-cardiovascular diseases, anticancer, anti-diabetic, anti-hepatoprotective, therapy of skin disorders and was used on personal care formulations. In fact, oleic acid the major fatty acid of MOSO is responsible for healthy Mediterranean diet, especially for the prevention of breast cancer. In addition, β-sitosterol structurally resembles cholesterol which has been proven to inhibit the intestinal absorption of cholesterol and elevates antioxidants making it effective antidiabetic, hypolipidemic, neuroprotective and chemopreventive agent. Now experimental studies on β-sitosterol gives clear evidence that the compound can be used as supplements to fight against life threatening diseases.

These properties allow to the valorization of *Moringa oleifera* seed oil at diverse industrial, medicinal, and pharmaceutical scales.

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Chapter 14
Bioactive Compounds of Cucurbitaceae Seed Oils as Nutraceuticals and Health-Promoting Substances

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ABSTRACT

Edible oils are one of the important products that have lately come to light for their beneficial and nutritional properties. As a result, scientists and the oil industry are always working to demonstrate the health-giving benefits of both fruit and vegetable seed oils. Fruits are popular for their fleshy parts. However, the seeds are often discarded since they are thought worthless. This research looked at the bioactive components found in Cucurbitaceae (Cucurbita spp., Cucumis melo L., Citrullus lanatus) seed oils extracted using various extraction procedures on Cucurbitaceae seeds from various species and geographical places throughout the globe. The outcomes of the study show that Cucurbitaceae seed oils are a good source of nutrients and may be classified as health-promoting compounds. The discoveries have also cleared the way for the use of these seed oil resources in the production of a broad variety of therapeutic products.

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INTRODUCTION

The scarcity of food resources, especially edible oils and fats, has forced an investigation into the potential of current edible oil sources. Fats and oils are a significant element of practically every civilization's diet. They are used in cooking, frying, baking, and so forth. Fats and oils have a significant nutritional function in the body. They provide a rich source of energy, fat-soluble vitamins, essential fatty acids, flavor transporters, and numerous bioactive chemicals that are required for various physiological activities. The seed oils have a broad variety of bioactivities, including antioxidant, antibacterial, and antiproliferative effects. Cucurbita crops are among the most frequent food items and raw materials used in the production of a broad variety of dietetic, medicinal, and preventive products (Piskunova and Mutyeva, 2016). Cucurbit seed oil is one of the most well-known products in the modern healthy nutrition market, particularly in Austria (Piskunova, 2015; Piskunova and Mutyeva, 2016). This oil is also gaining popularity in Russia and the former Soviet Union (Piskunova and Mutyeva, 2016). The use of cucurbit seed oil as a healthy diet component as well as for medicinal purposes is gaining popularity in China and Japan (Caili et al., 2006; Nishimura et al., 2014; Yao et al., 2019). The cucurbit seed oil is high in phytosterols, with β-sitosterol accounting for more than 39% of the total, and in carotenoids, with β-carotene and lutein being the primary components (Piskunova & Mutyeva, 2016; Ayyildiz *et al.,* 2019; Piskunova, 2015; Yao *et al.,* 2019). It is regarded as a one-of-a-kind treatment for preventing cardiovascular disease, hypertension, urogenital system disorders (prostatitis therapy), oncological and dermatological diseases (Orsavovà *et al.,* 2015). At the moment, there is an increasing need for medications made from natural substances, such as Cucurbitaceae seed oil. In compared to synthetic and semi-synthetic analogs, such medications are often more effective, safer, and less expensive (Bardaa et al., 2016; Piskunova & Mutyeva, 2016; Safar, 2019). The current chapter discusses the primary phytochemicals found in Cucurbitaceae seed oils produced by cold pressing or other methods, as well as their positive effects in promoting health and avoiding illness.

CUCURBITACEAE SEEDS AS POTENTIONAL SOURCES OF NEW TRENDS OF PLANT OILS

Cucurbitaceae seeds are considered as a rich source of oil (Al-Khalifa, 1996). The quantity of oil in the seeds is determined by a range of variables, including varietal and environmental conditions. The oil content of *Cucumis melo* seeds varied from 28.44 percent to 49.4 percent of dry weight (Rashwan *et al.,* 1993; De Melo *et al.,* 2000; Mallek-Ayadi *et al.,* 2019; Rezig *et al.,* 2019). Furthermore, for the species *Citrullus lanatus*, this concentration varied between 19.23 percent and 24.6 percent of the dry weight in watermelon seeds (Al-Khalifa, 1996; Rezig *et al.,* 2019). For the *Cucurbita pepo* species, pumpkin seeds contain between 29.33 percent and 51.01 percent oil by dry weight (El-Adawy & Taha, 2001; Nyam *et al.,* 2009; Meru *et al.,* 2018; Rezig *et al.,* 2019). Furthermore, for the species *Cucurbita moschata*, the oil content is around 44.42 percent of the dry weight (Al-Khalifa, 1996). Applequist *et al.* (2006) showed that the oil content in seeds ranged from 24.2 percent to 42.33 percent of dry weight for the species *Cucurbita maxima*.

Extraction and Processing of Cucurbitaceae Seed Oils

The quantity of oil extracted from Cucurbitaceae seeds varies depending on plant type, growing environment, ripening stage, seed harvesting time, and extraction technique used (Nyam *et al.,* 2009). Organic solvents are commonly used to extract lipids from oilseeds, but solvent extraction has some drawbacks, including the risk of thermal degradation of unsaturated fatty acids and functional compounds depending on the extracting conditions used, as well as the need to remove the organic solvent's residues from the oil (Bozan & Temelli, 2002).

Mechanical cold extraction of oils using an expeller is mostly utilized for fiber-rich sources with oil concentration more than 20%. However, as compared to solvent extraction, the expeller generally yields a lower extraction yield (10% -18% of the oil) (Carr, 1989). It is worth noting that in both cases, plant seed moisture should be reduced by sun-drying to facilitate extraction procedures.

To the best of our knowledge, the soxhlet device is the most often used method of extracting oil from Cucurbitaceae seeds. Nonpolar solvents such as n-hexane and chloroform are frequently used in such extraction techniques rather than petroleum ether (Al-Khalifa, 1996; Mariod *et al.,* 2009; Nehdi *et al.,* 2013). According to reports, the solvent/kernel ratio, rather than time and temperature, has the greatest influence on oil yield (Sultana & Ashraf, 2019).

Fatty Acid Composition and High Nutritional value factors of Cucurbitaceae seed oils

Fatty acid Composition

Cucurbitaceae (pumpkin, melon, and watermelon) seed oils are members of the oleic-linoleic acid group of oils, which also includes maize, sesame, sunflower, soya, and cottonseed oils. Table 1 summarizes the proximate fatty acid content of pumpkin seed oil (PSO), melon seed oil (MSO), and watermelon seed oil (WSO). Linoleic, oleic, palmitic, and stearic acids are the oil's primary fatty acids. Cucurbitaceae seed oils are a good supply of important fatty acids because to their high linoleic acid concentration. Numerous studies have shown a substantial link between dietary linoleic acid and blood cholesterol levels. A linoleic acid-rich diet helps to decrease plasma cholesterol and lowers the risk of cardiovascular disease (Heine *et al.,* 1989; Horrobin & Huang, 1987). Furthermore, linoleic acid is required for the synthesis of vitamin D, cellular membranes, and some hormones (Fruhwirth & Hermetter, 2007). Louheranta *et al.* (1996), on the other hand, proposed that a high linoleic acid consumption enhances the susceptibility of atherogenic lipoproteins to oxidation in males.

Minor bioactive lipids in Cucurbitaceae seed oils as nutraceuticals and health promoting substances

Sterols

Phytosterols are common components of plant cell walls. Because of their structural closeness to cholesterol, they inhibit cholesterol absorption from the stomach when consumed with plant meals. Purified plant sterols or stanols have been added to a variety of meals in recent decades to create functional foods with exceptional hypocholesterolemic action. According to Marangoni & Poli (2010), a daily consumption

Table 1. Fatty acid (%) composition of Cucurbitaceae seed oils.

	Cucurbita maxima		*Cucurbita pepo*		*Cucurbita moschata*	*Cucumis melo*		*Citrullus lanatus*	
	Rezig *et al.* (2012)[a]	**Rezig *et al.* (2018)[b]**	**Rabrenović, *et al.* (2013) [b]**	**Salgin and Kormaz (2011)[c]**	**Al-Khalifa (1996)[d]**	**var. 'Ananas' Rezig *et al.*, (2019)[b]**	**var. 'Maazoun' Mallek-Ayadi *et al.* (2012)[e]**	**var. 'Ananas' Rezig *et al.*, (2019)[b]**	**Górnaś & Rudzińska (2016)[e]**
Myristic acid (C14:0)	-	0.12 ± 0.00	-	-	0.16	tr.	0.04 ± 0.01	tr.	0.05 ± 0.00
Palmitic acid (C16:0)	15.97 ± 0.39	16.17 ± 2.32	11.2 ± 0.02	9.59 ± 0.94	13.1	14.43 ± 1.51	8.76 ± 0.07	9.88 ± 0.86	10.48 ± 0.06
Stearic acid (C18:0)	4.68 ± 0.56	8.57 ± 0.65	5.2 ± 0.08	7.46 ± 0.55	6.0	5.81 ± 0.62	5.64 ± 0.06	6.96 ± 0.71	7.37 ± 0.05
Oleic acid (C18:1)	44.11 ± 0.63	30.56 ± 2.87	39.2 ± 0.10	32.35 ± 0.85	26.2	23.52 ± 2.94	15.84 ± 0.03	14.25 ± 1.56	14.80 ± 0.09
Linoleic acid (C18:2)	34.77 ± 0.95	43.86 ± 5.24	44.5 ± 0.15	48.48 ± 0.63	53.2	59.26 ± 6.54	68.98 ± 0.05	68.07 ± 7.56	66.42 ± 0.18
Linolenic acid (C18:3)	tr.	-	0.2 ± 0.22	0.60 ± 0.20	0.12	0.22	0.20 ± 0.00	tr.	0.19 ± 0.00
Arachidonic acid (C20:0)	0.41 ± 0.40	0.60 ± 0.04	-	-	0.17	0.24 ± 0.02	0.16 ± 0.01	0.26 ± 0.03	0.31 ± 0.01
Gondoic acid (C20:1)	-	-	-	-	-	-	0.26 ± 0.01	tr.	0.10 ± 0.00
% Saturated fatty acids (SAFA)	21.07 ± 1.19	25.48 ± 2.33	16.4 ± 0.10	17.05 ± 1.49	19.71	20.24 ± 3.12	5.79	17.10 ± 1.85	-
% Monounsaturated fatty acids (MUFA)	44.12 ± 0.57	30.67 ± 2.78	39.2 ± 0.69	32.35 ± 0.85	26.64	23.52 ± 2.94	16.23	14.25 ± 1.87	-
% Polyunsaturated fatty acids (PUFA)	34.78 ± 0.85	43.86 ± 2.36	44.7 ± 0.78	49.08 ± 0.83	53.33	59.48 ± 6.34	69.18	68.07 ± 7.89	-

[a]: Seed oil obtained by cold extraction in petroleum ether;[b]: Cold-pressed seed oil; [c]: Supercritical CO_2 extraction; [d]: Seed oil obtained by cold extraction in chloroform/methanol 2:1; [e]: Seed oil obtained by cold extraction in hexane. SAFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty Acids; tr.: trace amounts (less than 0.2%). Values are means ± SD of three determinations; SD: standard deviation.

of plant sterols or stanols of 1.6-2 g/day, which are found in these foods, may lower cholesterol absorption from the gut by roughly 30% and plasma LDL cholesterol levels by 8-10%. Because the impact of plant sterols or stanols on plasma LDL cholesterol is additive to that of statins, the former may be used to boost the latter's hypocholesterolemic action in individuals who need a significant decrease in plasma LDL cholesterol levels. Phytosterols, at doses of up to 3 g per day, are both safe and effective cholesterol-lowering agents. Among the several plant sterols, β-sitosterol has received the most attention in terms of its physiological impact on human health. Many investigations have so proved sitosterol's beneficial qualities (Yang *et al.,* 2001). This phytochemical molecule is presently on the market and has been scientifically demonstrated to decrease low-density lipoprotein (LDL) cholesterol by 10% to 15% as part of a balanced diet (Ntanios, 2001). Rezig *et al.* (2019) reported a sterol content in "Ananas" variation of the Tunisian plant *Cucumis melo* L., belonging to the Cucurbitaceae family, of 5162 mg/kg oil. This content was higher in the cold pressed seed oil than in the "Maazoun" *Cucumis melo* L. and honeydew melon (*Cucumis melo*) seed oils found by Mallek-Ayadi *et al.* (2018) and Górnaś & Rudzińska (2016), respectively, and lower than that found by Veronezi & Jorge (2018) in the *Cucumis melo* var. "inodorus" seed oil obtained by n-hexane extraction. The primary sterols were β-sitosterol and Δ5-avenasterol, which accounted for 92.6 percent of total sterols in melon seed oil. β-sitosterol was also found in the seed oils of *Cucurbita maxima* var. "Béjaoui," *Cucurbita pepo* L., Kalahari melon (*Citrullus lanatus*), Bittermelon (*Momordica charantia* L.), *Cucumis melo* L., and watermelon (*Citrullus lanatus* (Thunb.) Matsum. & Nakai)

Tocopherols and tocotrienols (tocochromanols)

Tocopherols and tocotrienols, abbreviated as tocols, are natural lipophilic antioxidants that preserve vegetable oils from oxidation (Ozcan *et al.,* 2019; Schwartz *et al.,* 2008). Tocols (vitamin E) are composed of a chromanol ring with a C16 phytol side chain and are divided into two forms based on whether the side chain is saturated (tocopherols) or has three double bonds at carbons 3, 7, and 11 (tocotrienols) (Lachman *et al.,* 2018). Tocopherols and tocotrienols occur in four isomers known as alpha, beta, gamma, and delta; they vary in the methylation pattern of the benzopyran ring, which has three methyl groups (at C-5, C-7, and C-8) (Boschin & Arnoldi, 2011). The most potent lipid-soluble antioxidants in vegetable oils are alpha and gamma tocopherols. The strongest vitamin E activity is shown by alpha-tocopherol, whereas the highest antioxidant activity is shown by gamma-tocopherol (Böhmdorfer *et al.,* 2011; Boschin & Arnoldi, 2011). Recently, there has been a surge in interest in extracting oils from fruit seeds. The bulk of earlier research on fruit seed oils focused only on the fatty acid content. Similarly, there is little information on the profile of tocochromanols, particularly those identified in Cucrubitaceae seed oils. Table 27. 2a shows the tocopherol and tocotrienol compositions of *Citrullus lanatus* seed oils recovered using solvent and compression extraction procedures.

According to Górnaś *et al.* (2014), γ-T tocochromanol predominated in *Citrullus lanatus* (Thunb.) Matsum & Nakai seed oil, with a concentration 25 times greater than that found for α-T. Nonetheless, watermelon seeds contained trace quantities of β-T, γ-T, α-T3, and γ-T3. Similarly, only a high level of α-T and a low quantity of δ-T were discovered in the seeds of four distinct watermelon cultivars cultivated in Pakistan (Raziq *et al.,* 2012). However, Górnaś *et al.* (2014) discovered a comparable tocochromanol composition in Kalahari melon seeds from northern Namibia and *Citrullus lanatus* (Thunb.) Matsum & Nakai seeds from Brazil (Nyam *et al.,* 2009; de Conto *et al.,* 2011). The high amount of γ- tocopherol is consistent with the findings of Mariod *et al.* (2009), Jorge *et al.* (2015), and Angelova-Romova *et al.* (2019). They all claimed that γ-tocopherol was the dominant nutrient. According to Rossel (1991), the initial content of tocopherols may range from a few mg kg^{-1} to several hundred mg kg^{-1} depending on the oil type and fatty acid composition. It should be noted that there is relatively little information available on the tocopherol content of cold pressed watermelon seeds. According to our knowledge, de Conto *et al.* (2011) were the first to compare the tocopherol concentrations of watermelon seeds extracted chemically by solvent and mechanically by an expeller. The authors also stated that the extraction process had no effect on the preservation of beneficial components such tocopherols ($p \leq 0.05$). Table 27. 2b shows the tocopherol and tocotrienol content of *Cucumis melo* L. seed oils derived by solvent extraction techniques and accessible in the literature.

As shown, γ-tocopherol was the most abundant tocopherol in all samples, accounting for 78.21 percent and 100 percent of total tocopherols in the *Cucumis melo* var. 'Agrestis' coming from Gezira in Sudan, and in the same variety; whose fruits were purchased from a local market in Khartoum North (Sudan) respectively (Azhari *et al.,* 2014; Mariod *et al.,* 2009). Petkova & Antova (2019) corroborated the discovery in melon seed oil, where γ-tocopherol accounted for 87.8 percent of total tocopherols. According to Fatnassi *et al.* (2009), α-tocopherol is suggested for human and animal consumption since it has greater biological activity than other tocopherols. However, γ-tocopherol has a stronger antioxidant capacity than α-tocopherol. The total tocols content of pumpkin seed oil ranges from 265.7 mg/kg to 977.9 mg/kg (Akin *et al.,* 2018; Vujasinovic *et al.,* 2012). The predominant tocopherol isomer is γ-tocopherol, which accounts for over 90% of total tocopherols in cold pressed pumpkin seed oil. This tocopherol isomer's concentration may vary between 251 mg/kg and 775 mg/kg. α-tocopherol is the second most

prevalent tocol, with concentrations ranging from 10.1 mg/kg to 353 mg/kg (Broznić *et al.,* 2016; Naziri *et al.,* 2016). Pumpkin seed oil contains trace levels of β- and δ-tocopherols (Rabrenović *et al.,* 2014; Vujasinovic *et al.,* 2012). In addition to tocopherols, cold pressed oils of pumpkin seeds cultivated in Turkey included α-, β-, and γ-tocotrienols (Akin *et al.,* 2018). While Naziri *et al.* (2016) proposed that α- and γ-tocopherol increase the oxidative stability of pumpkin seed oil, Gorjanović *et al.* (2011) found strong positive correlations between δ-tocopherol content and DPPH and H_2O_2-scavenging activities of cold pressed pumpkin seed oil ($r = 0.89$ and $r = 0.87$, respectively).

Phenolic Compounds

In recent years, there has been an increase in interest in researching phenolic chemicals derived from oilseeds, their skins, hulls, and oil cake meals. This interest stems from the fact that these chemicals have the ability to improve one's health (Peschel *et al.,* 2006; Wang *et al.,* 2007). Vanillic acid (11.4 g/100 g), p-coumaric acid (3.8 g/100 g), ferulic acid (3.8 g/100 g), and protocatechuic acid (3.1 g/100 g) were found in *Cucurbita pepo* seed oil by Siger *et al.* (2008). Furthermore, Rezig *et al.* (2012) discovered six phenolic acids in *Cucurbita maxima* var. "Béjaoui" seed oil extracted by petroleum ether: syringic acid (7.96 mg/100g), ferulic acid (4.99 mg/100g), caffeic acid (3.88 mg/100g), *p*-coumaric acid (2.5 mg/100g), vanillic acid (2.46 mg/100g), and protocatechuic acid (1.81 mg/100g). Caffeic acid (3.4 - 3.8 mg/100 g) and syringic acid (7.6 - 8 mg/100 g) were found in pumpkin seed oils derived from Turkey seeds, according to Akin *et al.* (2018). Regarding watermelon seed oil, Rezig *et al.* (2019) discovered two kinds of phenolic chemicals, including phenolic acids and lignans, in the cold pressed var. "Crismon" seed oils, which are represented by caffeic acid (1.33 mg/g) and pinoresinol (1.02 mg/g). Caffeic acid (0.41 mg/100g) was found in melon seed oil by Nyam *et al.* (2009), followed by vanillic acid (0.55 mg/100g), gallic acid (0.23 mg/100g), p-hydroxybenzoic acid (0.21 mg/100g), p-coumaric acid (0.18 mg/100g), ferulic acid (0.17 mg/100g), and protocatechuic acid (0.05 mg/100g).

Total Phenolics and Flavonoid Contents

The total phenolic and flavonoid content of Cucurbitaceae seed oils is little documented in the scientific literature. Hashemi *et al.* (2017) found watermelon *Citrullus lanatus* seed oil to have a total phenolic content (TPC) of 111 mg gallic acid equivalent (GAE) per kilogram of oil. This level was lower than that found in *Citrullus lanatus* seed oil (1428.9 mg GAE/kg), *Cucumis melo* "Maazoun" variety (226 mg GAE/Kg), and yellow melon (*Cucumis melo* var. 'inodorus Naudin') (130.7 mg GAE/kg) (da Silva & Jorge, 2014; Jorge *et al.,* 2015; Mallek-Ayadi *et al.,* 2019). TPC variations may be related to variations in Cucurbitaceae cultivars, growth circumstances, and the polarity of the extraction solvents (Rahman *et al.,* 2013). When compared to soybean, sunflower, rapeseed, maize, grapeseed, hemp, flax, and rice bran cold pressed oils, pumpkin seed oil has a significantly high TPC (Siger *et al.,* 2008). TPC levels in pumpkin seeds ranged from 4.63 mg GAE/kg to 2240 mg GAE/kg (Aktaş *et al.,* 2018; Vujasinovic *et al.,* 2012). Flavonoids, on the other hand, are the most frequent and extensively dispersed plant phenolic chemical group. They are essential for plant development and protection against infection and injury. Because of their considerable antioxidant and chelating characteristics, these plant secondary metabolites have been found to have a broad spectrum of antiallergic, antiinflammatory, antibacterial, and anticancer actions (Heim *et al.,* 2002; Khatiwor *et al.,* 2010). Morais *et al.* (2015) found 24.7 mg quercetin equivalent (QE) and 3.61 mg QE per 100g of dry weight seeds in watermelon (*Citrullus lanatnus*) and

Table 2a. Tocopherol and tocotrienol composition of Citrullus lanatus seed oils (mg/kg).

Sample	Origin	Extraction procedure	α-T	β-T	γ-T	δ-T	α-T3	β-T3	γ-T3	δ-T3	Reference
Citrullus lanatus (Thunb.) Matsum. & Nakai	Brazil	n-hexane	1.68 ± 0.29	-	62.83 ± 10.12	0.69 ± 0.05	ND	ND	ND	ND	de Conto *et al.* (2011)
		Expeller	1.43 ± 0.38	-	71.07 ± 11.15	0.69 ± 0.07	ND	ND	ND	ND	
Citrullus lanatus (Thunb.) Matsum. & Nakai	Latvia	*n*-hexane-ethyl acetate (9:1; v/v)	12.9 ± 3.0	0.6 ± 0.1	313 ± 10.2	7.2 ± 0.5	0.4 ± 0.1	-	0.5 ± 0.1	-	Górnaś *et al.* (2014)
Kalahari melon *(Citrullus lanatus)*	Namibia	Soxhlet extractor (Petroleum ether)	259.4 ± 26.8	32.7 ± 3.0	705.6 ± 6.6	93.3 ± 9.3	ND	ND	ND	ND	Nyam *et al.* (2009)
Citrullus lanatus var. Sugar Baby	Pakistan	Soxhlet extractor (n-hexane)	195.6 ± 12.2	-	-	12.3 ± 0.9	ND	ND	ND	ND	Raziq *et al.* (2012)
Citrullus lanatus var. Q-F-12			164.3 ± 5.6	-	-	58.3 ± 1.2	ND	ND	ND	ND	
Citrullus lanatus var. D-W-H-21			122.0 ± 7.1	-	-	9.1 ± 0.5	ND	ND	ND	ND	
Citrullus lanatus var. Red Circle - 1885			120.6 ± 10.25	-	-	20 ± 1.1	ND	ND	ND	ND	
Citrullus colocynthoides	Sudan	Soxhlet extractor (Petroleum ether)	-	-	359 ± 2.1	10 ± 1.0	ND	ND	ND	ND	Mariod *et al.* (2009)

T: Tocopherol; T3: Tocotrienol; Values are means ± SD of three determinations; SD: standard deviation; ND: Not Determined.

melon (*Cucumis melo*) seed oils, respectively. The results are obviously lower than those reported by Mallek-Ayadi *et al.* (2018) in melon seeds (87.52 mg QE/100g). Another research discovered that the total flavonoid content of watermelon seeds was 3.06 mg catechin per milligram (Mehra *et al.,* 2015).

Carotenoids

Carotenoids are lipophilic compounds found in seed oils. These bioactive chemicals have antioxidant characteristics because they are effective singlet oxygen quenchers and chain-breaking antioxidants, protecting cells and other bodily components from free radical damage (Murkovic *et al.,* 2002). Carotenoids have also been linked to several health advantages, including the prevention of cardiovascular disease, prostate cancer, and macular degeneration (Silva *et al.,* 2018; Stahl & Sies, 2005). In terms of nutrition, these pigments are said to be high in vitamin A, in addition to their antioxidant characteristics (Mallek-Ayadi *et al.,* 2019).

Total carotenoid content in cold pressed pumpkin seed oil (*Cucurbita pepo* L.) was estimated to be between 69 mg/Kg and 228 mg/Kg by Özbek & Ergönül (2020). According to Tuberoso *et al.* (2007), cold pressed pumpkin seed oil had more -carotene than flaxseed, grapeseed, maize, peanut, rapeseed, soybean, and sunflower cold pressed oils, but less than virgin olive oil. The carotenoid content of *Cucumis melo* has been observed to range between 2.43 and 38.5 mg/kg. This amount was comparable to

Table 2b. Tocopherol and tocotrienol composition of Cucumis melo L. seed oils (mg/100g).

Sample	Origin	α-T	β-T	(β+ γ)-T	(β+ δ)- T	γ-T	δ-T	α-T3	β-T3	γ-T3	δ-T3	Reference
Cucumis melo Var. 'Maazoun'	Tunisia	2.85 ± 0.17	-	18.13 ± 0.41		6.09 ± 0.53	-	ND	ND	ND	ND	Mallek-Ayadi *et al.* (2018)
Cucumis melo var. 'flexuosus'	Sudan	0.4 ± 0.05	-	-	-	33.5 ± 0.26	0.8 ± 0.05	ND	ND	ND	ND	Mariod *et al.* (2009)
Cucumis melo var. 'agrestis'		-	-	-	-	29.1± 0.6	-					
Cucumis melo var. 'Inodorus'	Brazil	3.98 ± 0.02	-	-	-	46.77± 0.04	ND	ND	ND	ND	ND	Veronezi & Jorge (2018)
Canary melon (*Cucumis melo* L.)	Spain	6.88 ± 0.61	-	-	-	63.08 ± 0.75	0.77 ± 0.03	0.47 ± 0.02	-	0.9 ± 0.03	-	Górnaś *et al.* (2015)
Yellow melon *Cucumis melo* var. 'inodorus Naudin'	Brazil	2.05 ± 0.03	-	-	-	24.96 ± 0.00	ND	ND	ND	ND	ND	da Silva & Jorge (2014)
Cucumis melo var. '*tibish*'	Sudan	2.7 ± 0.17	-	-	-	13.1 ± 0.41	27.4 ± 0.53	ND	ND	ND	ND	Azhari *et al.* (2014)
Cucumis melo var. 'agrestis'	Sudan (Ghibaish)	7.21 ± 0.1	-	-	-	32.2 ± 0.1	0.17 ± 0.03	-	0.33 ± 0.2	-	-	Mariod & Matthäus (2008)
Cucumis melo var. 'agrestis'	Sudan (Gezira)	8.21 ± 01	-	-	-	30.2 ± 0.2	0.2 ± 0.1	-	0.3 ± 0.05	-	-	Mariod & Matthäus (2008)

ND: not determined.

that of watermelon seed oil (*Citrullus lanatus*), which had a carotenoid level ranging from 6.3 to 39.1 mg/kg (de Conto *et al.,* 2011; Szydlowska-Czerniak *et al.,* 2011; da Silva & Jorge, 2014).

Chlorophylls

One of the most common pigments in edible oils, chlorophylls, may operate as an antioxidant in lipid auto-oxidation while also acting as a sensitizer and producing singlet oxygen molecules in the presence of light (Choe, 2017). Cold pressed pumpkin seed oil has chlorophyll levels equivalent to virgin olive oil (30.8 mg/kg and 33.9 mg/kg, respectively) (Tuberoso *et al.,* 2007). Mallek-Ayadi *et al.* (2019) found a total concentration of 5.70 mg/kg of chlorophyll in melon seed oil.

BIOLOGICAL ACTIVITIES OF CUCURBITACEAE SEED OILS

Antioxidant activities

According to Silva *et al.* (2018), the presence of certain chemicals, such as phenolics and flavonoids, is primarily responsible for seed oil's antioxidant activity. Other research has shown that certain fatty acids and trace components, such as linoleic acid, are relevant in terms of oil antioxidant action (Ramaprasad *et al.,* 2006). The hydrogen-donating antioxidants model's antiradical activity is commonly utilized to test antioxidant characteristics in a relatively short period. The DPPH free radical scavenging test is often used to measure this capacity. In this context, IC_{50} refers to the sample concentration necessary to scavenge 50% of DPPH radicals. Thus, a low IC_{50} corresponds to a strong scavenging capability, and

it is evaluated by graphing percentage inhibition against various oil concentrations (Guergouri *et al.,* 2017). Cold pressed Cucurbitaceae seed oils were tested for antiradical activity by Rezig *et al.* (2019). *Cucumis melo* var. 'Ananas,' *Citrullus lanatus* var. 'Crimson,' and *Cucurbita pepo* var. 'Essahli' all had IC_{50} values of 52.55 ± 5.08 g/g, 159.64 ± 15.47 g/g, and 64.71 ± 6.07 g/g, respectively. Furthermore, Azhari *et al.* (2014) showed Seinat (*Cucumis melo* var. "*tibish*") seed oil to have stronger antioxidant activity than Rezig *et al.* (2019), with an IC_{50} of 25.2 mg/mL. When compared to cold pressed 'Essahli' *Cucurbita pepo* L. and 'Crimson' *Citrullus lanatus* seed oils, *Cucumis melo* var. 'Ananas' seed oil had the best antioxidant activity. Casoni *et al.* (2019) classified PSO (IC_{50} = 36.2 percent) as a "medium DPPH radical scavenging activity oil," along with oils of chia seed (IC_{50} = 30.4 percent), apricot seed (IC_{50} = 38.8 percent), sunflower seed (IC_{50} = 25.7 percent -39.3 percent), linseed (IC_{50} = 32.7 percent), argan seed (IC_{50} = 31.5 percent), mustard seed (IC_{50} = 34.6%), red grape seed (IC_{50} = 33.7%), almond seed (IC_{50} = 25.3%), rapeseed (IC_{50} = 35.1%), walnut (IC_{50} = 36.2%), negrilic (IC_{50} = 33%), and sesame seed (IC_{50} = 36.9%). The DPPH radical scavenging activity of these seed oils was mostly determined by the content of tocochromanols. Górnaś *et al.* (2015) discovered a substantial association (R^2 = 0.994) between the overall concentration of tocochromanols in seed oils and the DPPH radical scavenging activity. This finding shows that various tocopherol and tocotrienol homologs quench DPPH free radicals with comparable potency.

Anti-inflammatory activities

Many chronic illnesses, including rheumatoid arthritis, are caused by oxidative stress and inflammation (RA). The impact of oxidative stress in the onset and development of joint disorders cannot be overstated (Knight, 2000). ROS (reactive oxygen species) cause oxidative damage that accumulates throughout the life cycle. It is worth noting that radical-related damage affects DNA, proteins, and lipids, all of which have been implicated in the development of arthritis. Arslanbaş *et al.* (2020) investigated the anti-inflammatory potential of pumpkin seed oil. The authors observed that injecting carrageenan into the hind paws of rats enhanced vascular permeability and/or blood flow, causing edema to expand in size in all treatment groups and initiating the vascular phase of the inflammatory process. Pro-inflammatory cytokines such as TNF-, IL-6, and IL-1, as well as histamine and serotonin, are inflammation mediators that are produced during the first hour of the vascular phase (first phase). These mediators are responsible for rashes, edema, and secretions (Al-Zuhair *et al.,* 1997; Ben Khedir *et al.,* 2016). The inflammation persisted, intensifying and reaching a climax in the second hour. The findings indicated that Turkey PSO (40 and 100 mg/kg dosages) inhibited rat paw edema over time. According to this circumstance, PSO has an antagonistic impact on all inflammatory mediators in the vascular and cellular phases. PSO dosages of 40 and 100 mg/kg were observed to substantially lower the percentage of inflammation in the fourth hour ($p < 0.05$). Al-Okbi *et al.* (2016) performed a research comparing the anti-inflammatory properties of Egyptian and European kinds of PSO in a rat adjuvant arthritis model, and their findings were congruent with those of Arslanbaş *et al.* (2020).

THERAPEUTIC EFFECTS OF CUCURBITACEAE SEED OILS

Anti-hypertensive and Anti-cardiovascular Affects

Pumpkin seed oil (PSO) and watermelon seed oil (WSO) were shown to have antihypertensive, cardioprotective, and antihypercholesterolemic effects by El-Mosallamy *et al.* (2012) and Eke *et al.* (2021). In fact, PSO greatly decreased the rise in systolic blood pressure by L-NAME and normalized the L-NAME-induced electrocardiogram changes. When compared to the L-NAME-treated group, PSO considerably reduced the raised levels of plasma malondialdehyde, a hallmark of lipid peroxidation, increased oxidative stress, and reverted the lowered levels of nitric oxide metabolites to near normal levels. When compared to the olive oil-treated group, WSO doses of 2 mL/kg and 5 mL/kg substantially reduced blood cholesterol, triglyceride, and LDL (low density lipoprotein), but increased HDL (high-density lipoprotein) and VLDL (very low density lipoprotein). According to the scientists, the considerable decrease in cholesterol levels discovered suggests that consuming WSO regularly for 28 days may suppress 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, a rate-limiting enzyme in cholesterol production (Okediran *et al.,* 2015). These results are consistent with those obtained from experimental animals given a diet supplemented with Egusi melon seed oil for six weeks (Eidangbe *et al.,* 2010; Francis *et al.,* 2019).

Anti-diabetic Effet

Eke *et al.* (2021) investigated the anti-diabetic properties of watermelon seed oil (WSO) in albino rats. To that end, thirty Wistar albino rats were split into five groups of six individuals each (A-E; n = 6). Group A acted as the control group, receiving just chow and water; groups B and C got 2 mL/kg and 5 ml/kg of WSO, respectively, while groups D and E received 2 mL/kg and 5 mL/kg of olive oil (Goya extra virgin), respectively, once daily for 28 days. Because of its capacity to prevent hepatic fibrosis and damage in rats, olive oil was selected as a standard oil. The oils used in this research (WSO and olive oil as a control) were given by gastro-oral gavage. On days 8 and 15 of therapy, the oral glucose tolerance test (OGTT) was performed. After fasting overnight, the animals were administered an oral glucose load of 300 mg/kg body weight. A glucometer was used to measure the glucose levels in the rats' tail vein at 0, 15, 30, 45, and 60 minutes. In the first and second weeks of the trial, blood glucose levels in the temoin, watermelon seed oil, and olive oil treatment groups dramatically increased after 30 minutes of loading with 300 mg/kg glucose solution. Oral treatment of WSO and olive oil to rats enhanced glucose tolerance at 60 minutes due to increased glucose absorption from the gastrointestinal tract as compared to the healthy untreated group. Sebbagh *et al.* (2009) observed a comparable finding in a healthy and diabetic model of rats on a diet supplemented with *Citrullus colocynthis*, sunflower, and olive oils. These results suggested that watermelon seed oil and olive oil had the capacity to decrease postprandial glucose increase in diabetic subjects, presumably owing to their high linoleic acid content.

Anti-prostate Effect

The benefits of pumpkin seed oil derived from *Cucurbita pepo* (CP) oil were studied in a clinical study involving approximately 2000 males suffering from benign prostatic hypertrophy (BPH) (Friederich *et al.,* 2000). The authors demonstrated that an oral administration of 500-1000 mg/day of CP oil for 12

weeks reduced the International Prostate Symptom Scores by 41.4 percent and that more than 96 percent of the patients experienced no adverse effects, indicating that CP oil significantly improved urinary dysfunction in patients (Friederich *et al.,* 2000). Gossell-Williams *et al.* (2006) discovered that CP oil prevented testosterone-induced prostate hypertrophy in rats. In this study, rats given 0.3 mg/100 g body weight of testosterone experienced an increase in prostate size ratio, which was prevented by giving them 2.0 or 4.0 mg/100 g body weight of CP oil. Similarly, Nishimura *et al.* (2014) investigated the impact of another pumpkin seed oil, *Cucurbita maxima* (CM oil). Authors found that CM oil was safe, well tolerated, and helpful in avoiding urinary problems such as overactive bladder (OAB) and benign prostatic enlargement in these investigations (BPH). These effects were linked to the CM oil's sitosterol concentration, showing its potential for the prevention or treatment of urinary diseases such as OAB. In the same study, Hong *et al.* (2009) investigated the effects of pumpkin seed oil and saw palmetto oil on symptomatic benign prostatic hyperplasia in Korean males. These trials found that patients who received pumpkin seed oil, saw palmetto oil, or a combination of pumpkin seed oil and saw palmetto oil for more than a year improved in benign prostate hypertrophy (BPH) symptoms when compared to those who received a placebo. While the therapeutic effectiveness of this two-oil combination did not increase, no negative effects were identified. According to the findings of these researches, pumpkin seed oil and saw palmetto oil are clinically safe and may be useful as supplemental and alternative therapies for the treatment of BPH.

Hepatoprotective Effect

Citrullus lanatus seed oil; CLSO (125 mg) and CLSO (250 mg) were given orally to CCl4-induced rats for 10 days and compared to normal silymarin (100 mg/kg) orally. ALT (alanine aminotransferase), AST (aspartate aminotransferase), and ALP (alkaline phosphatase) values, which were elevated owing to CCl4-induced liver damage, drop considerably among the treated groups and are equivalent to the standard medicine silymarin (Madhavi *et al.,* 2012). Oluba *et al.* (2008) investigated Egusi melon seed oil (EMO). The extracted oil was employed in diet formulation and given to rats for 6 weeks (as a supplement to a cholesterol-based diet) to examine its influence on blood activities of LDH (Lactate dehydrogenase), ALT, AST, and γ-GT (gamma-glutamyltranspeptidase). The serum activities of the enzymes were significantly reduced ($p < 0.05$) in rats given Egusi melon oil.

Beneficial Effects on Skin Care

Previous research has demonstrated that treating skin lesions with Cucurbitaceae seed oil with a high level of polyunsaturated fatty acids (PUFAs) (more than 50% of total fatty acids) enhances wound healing and inflammation elimination (Bardaa *et al.,* 2016; Safar, 2019). Bardaa *et al.* (2015) performed a research to evaluate the therapeutic properties of pumpkin and linseed oils. The experiment was carried out on rats with second-degree burns. The findings revealed that rats given linseed, pumpkin, and "CytolCentella®" had a larger percentage of wound contraction (98.68, 96.71, and 92.54 percent, respectively) than the control group (58.38 percent). Biopsies histomorphometric study demonstrated that pumpkin oil and CytolCentella® may considerably boost collagen formation by 64.9 percent and 61.2 percent, respectively. Nakai (Kalahari melon) seed oil was also researched for its ability to preserve good skin. In reality, melon seed oil includes a variety of fatty acids that may be useful when applied to the skin topically. Komane *et al.* (2017) investigated the safety (irritancy potential test) and effectiveness (tran-

sepidermal water loss, hydration, and occlusivity tests) of topically administered Kalahari melon seed oil on healthy Caucasian adult female volunteers (n = 20). When used topically, Kalahari melon seed oil did not irritate the skin (observed at 24, 48, 72 and 96 h). The irritancy level findings demonstrated that using Kalahari melon seed oil decreased transepidermal water loss and boosted moisture retention.

Effect on Sex Hormones

The impact of various traditionally derived edible seed oils (sesame, peanut, and melon oils) on albino wistar rats' sex hormones - prolactin, progesterone, testosterone, estradiol, luteinizing hormone (LH), and follicle stimulating hormone (FSH) - was investigated. The findings showed that supplementing with 5% and 10% *Citrullus lanatus* seed oil induced a substantial rise ($p < 0.05$) in prolactin (with a corresponding drop in progesterone), LH, estradiol, and testosterone compared to the controls (Agiang *et al.,* 2015).

Effects of Pumpkin Seed Oil in Cancer Models

Plant chemicals that have structural and functional similarities to mammalian estrogens and can bind to mammalian estrogen receptors are known as phytoestrogens (Benassayag *et al.,* 2002). Because of their mild inhibitory action on aromatase, phytoestrogens may influence the risk of breast cancer (Lacey *et al.,* 2005). Importantly, low to high intake of pumpkin seeds, as well as soybeans and sunflower seeds, was linked to a considerably decreased risk of breast cancer (Zaineddin *et al.,* 2012). A population-based case-control study of postmenopausal German women looked at the relationship between phytoestrogen-rich foods and dietary lignans and breast cancer risk. Data on dietary profiles were acquired from 2,884 cases and 5,509 controls using a validated food frequency questionnaire that included extra items on phytoestrogen-rich foods. The findings offered support for a decreased incidence of postmenopausal breast cancer related with higher intake of sunflower, pumpkin, and soybean seeds (Zaineddin *et al.,* 2012). Richter *et al.* (2013) investigated the effects of phytoestrogen extracts extracted from pumpkin seeds on estradiol synthesis and ER/PR expression in breast cancer and trophoblast tumor cells, as enhanced estradiol production was recorded in MCF7, BeWo, and Jeg3 cells in a dose dependent manner. MCF-7 cells treated with varied doses of estradiol (10, 50, and 100 g/mL) exhibited the same pattern of ER and PR expression. However, ERα expression was greatly reduced, ERβ expression remained unchanged, and PR expression was increased (Richter *et al.,* 2013). The levels of ERα, ERβ, and PR expression in Jeg-3 and BeWo cells did not alter substantially when treated with pumpkin seed extract vs. untreated cells (Richter *et al.,* 2013). Nonetheless, further in-depth preclinical research is needed to investigate the possible function of pumpkin seed lignans in breast cancer prevention and/or therapy. Plant new ribosome-inactivating proteins (RIPs) have been shown to have antiviral, antifungal, and insecticidal effects. As a result, they may play essential roles in the plant defense system and have a high potential for medical or agronomic uses, such as anticancer medicines or antiviral transgenic tobacco (Krishnan *et al.,* 2002). Moschatin, a new RIP, has been isolated and described from ripe pumpkin seeds (*Cucurbita moschata*) (Xia *et al.,* 2003). Using the anti-human melanoma McAb Ng76, a new immunotoxin Moschatin-Ng76 was successfully synthesized, which effectively reduced the development of targeted melanoma cells M21 with an IC_{50} of 0.04 nM, which is 1500 times lower dosage than that found with free Moschatin (Xia *et al.,* 2003). These findings suggest that Moschatin might be employed as a novel and effective chemopreventive drug against melanoma (Xia *et al.,* 2003).

Pumpkin Seed Oil Extracted from *Cucurbita maxima* Improves Urinary Disorder in Human Overactive Bladder (HOB)

Nishimura *et al.* (2014) investigated the impact of *Cucurbita maxima* pumpkin seed oil on urinary dysfunction in overactive bladder patients (OAB). This research included 45 participants (male: female ratio = 25:20; ages 41-80 years). For 12 weeks, an extract of pumpkin seed oil from *Cucurbita maxima* (10 g oil/day) was taken orally. Urinary function was assessed after 6 and 12 weeks using the Overactive Bladder Symptom Score (OABSS). The individuals' OABSS was dramatically lowered by pumpkin seed oil derived from *Cucurbita maxima*. Such findings imply that pumpkin seed oil extracts from *Cucurbita maxima* and *Cucurbita pepo* are beneficial for urinary diseases such as OAB in people. Although the molecular mechanism of the seed oil for the alleviation of urinary tract problems is not fully known, Friederich *et al.* (2000) hypothesize that sitosterols found in the seed oil are responsible for alleviating these disorders.

CONCLUSION

Cucurbitaceae seed oils have been shown to have a variety of nutritious and bioactive components. They possess a high concentration of biologically active substances such as oleic and linoleic acids, phenolic compounds, flavonoids, tocopherols, and sterols, which have a favorable impact on humans. The percentages varied based on the place where the seeds were grown and the sorts of seeds analyzed. The existence of bioactive chemicals is completely supported by their health advantages, which include anti-inflammatory, hypoglycemic, hepatoprotective, and anticancer properties, as well as an intriguing antioxidant potential. As a result, in the near future, several industries, including food and pharmaceuticals, will use the Cucurbitaceae seeds as a raw material, resulting in mass production of oils and dietary supplements. This book chapter is intended to serve as a starting point for further research into Cucurbitaceae seed oils based therapeutic product formulations.

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Chapter 15
Experimental Informational Compilation on Isolation From Herbal Sources and Biological Activity of Rosmarinic Acid

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ABSTRACT

Rosmarinic acid is a valuable polyphenolic molecule mainly found in species of Boraginaceae and Lamiaceae. The amount of rosmarinic acid varies according to the environmental condition in which the plant grows, temperature, and humidity. The content of 0.01 to 72 mg/g of rosmarinic acid has been determined in various plants. Biotechnological production of rosmarinic acid by plant cell culture is recommended for its high production. The investigations have mainly addressed sources of rosmarinic acid, its production, and its biological effects. It has antioxidant, anti-inflammatory, antiviral, and anti-cancer activities, and it is an important substance for the pharmaceutical, food, and cosmetic industries. In addition to its antioxidant effects, it has been tested in recent studies in neurodegenerative diseases and has been found to have beneficial effects in these diseases, especially on memory. In this chapter, attention was drawn to the importance of rosmarinic acid, a valuable chemical, and general information about its phytochemistry, production, and biological activities was reviewed.

INTRODUCTION

Rosmarinic acid is an ester of caffeic acid and 3, 4-dihydroxyphenylactic acid (Figure 1). It is known to be a secondary metabolite that acts as a defense agent in plants. The discovery of Rosmarinic acid dates back to the 1950s. The pure compound was named Rosmarinic acid because it was first isolated from

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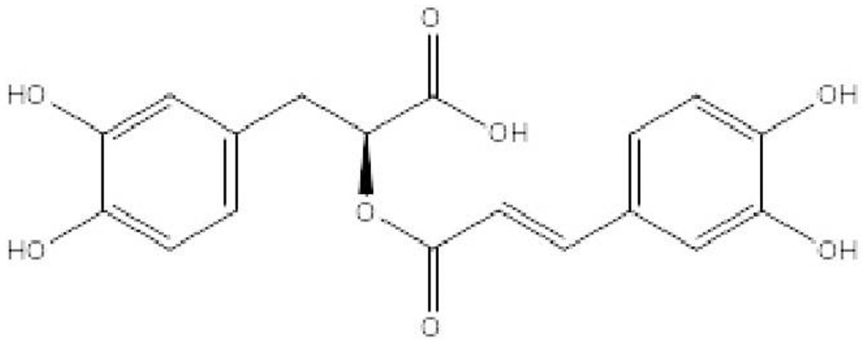
Figure 1. Rosmarinic acid



Rosmarinus officinalis. The amount of Rosmarinic acid varies according to the environment in which the plant grows, temperature and humidity. It was found that the amount of Rosmarinic acid increased in the presence of fungal infections in species containing Rosmarinic acid. It has been found that Rosmarinic acid content of more than 3% by dry weight is required for medicinal use of species containing this compound. The content of 0.01 to 72 mg/g Rosmarinic acid has been determined in some plants. Some species in family Labiatae were studied and found that *Mentha spicata* has the highest amount of Rosmarinic acid (Shekarchi *et al.,* 2012).

Various extraction, separation and chromatographic methods have been developed to optimize the extraction and identification of Rosmarinic acid. Solvent type, temperature, extraction time, particle size and solvent ratio of the material to be extracted are some of the parameters examined. Studies with plant cell cultures, for example *Coleus blumei* or *Salvia officinalis*, yielded much higher amounts of Rosmarinic acid than from plants (up to 36% of the dry weight of the cell). Therefore, biotechnological production of Rosmarinic acid by plant cell culture is recommended (Petersen & Simmonds, 2003).

Most studies on Rosmarinic acid have focused on its antioxidant and anti-inflammatory effects. It has been found that Rosmarinic acid can be a good preservative especially for food. In recent years, important studies have been conducted, especially in the field of neurodegenerative diseases, and attempts have been made to clarify the mechanism of these diseases. Since the possibility of free radical formation could be the cause of these diseases, Rosmarinic acid has been found to alleviate motor neuron degeneration, especially in studies conducted in Alzheimer's disease and ALS. These studies have shown that Rosmarinic acid is one of the important molecules that can provide additional benefits for treatment with a neuroprotective effect. Rosmarinic acid has been studied in animal experiments and clinical trials in the field of antioxidants, antiinflammatory, antiviral, anticancer, antiallergic, photoptotective effects as well as neurodegenerative diseases and others. It has been found that Rosmarinic acid is suitable for daily use. Studies on its effects on physiological and pathological conditions and possible protective effects on diseases are still ongoing (Rampart *et al*., 1986; Petersen & Simmonds, 2003; Takano *et al*., 2004; Psotova *et al*., 2006; Swarup *et al.,* 2007; Fkui *et al.,* 2009; Friedman, 2015).

Rosmarinic acid is rapidly absorbed, methylated, and eliminated in the urine, according to metabolism studies, and the majority of Rosmarinic acid and its metabolites are excreted in the urine. Studies on the toxicity of Rosmarinic acid have shown that it has very low toxicity with an LD_{50} around 561 mg/

kg in mice. In human studies, no abnormalities were observed in whole blood counts, liver and kidney function tests at doses up to 500 mg/day (Friedman, 2015).

This section briefly presents the phytochemical and pharmacological importance of Rosmarinic acid using main literature knowledge.

BACKGROUND AND MAIN FOCUS OF THE CHAPTER

Rosmarinic acid is frequently found in the Boraginaceae and Lamiaceae families. It has also been identified in other families (Acanthaceae, Amaranthaceae, Apiaceae, Araceae, Araliaceae, Asteraceae, Boraginaceae, Brassicaceae, Cannaceae, Celastraceae, Crassulaceae, Cucurbitaceae, Cyperaceae, Dipsacaceae, Fabaceae, Iridaceae, Lamiaceae, Linderniaceae, Malvaceae, Marantaceae, Melianthaceae, Moraceae, Myrtaceae, Onagraceae, Plantaginaceae, Poaceae, Polygonaceae, Portulacaceae, Potamogetonaceae, Rosaceae, Rubiaceae, Sapindaceae, Scrophulariaceae, Solanaceae, Zosteraceae etc.). For example, it has been found in ferns of the Blechnaceae family, in lower plants such as Anthocerotophyta, in marine plants, in monocotyledonous plants such as Potamogetonaceae and Cannaceae. Therefore, Rosmarinic acid is not a marker compound for chemotaxonomic studies. Before the structure of Rosmarinic acid was fully elucidated, the expression "Labiatengerbstoffe" (Lamiaceae tannin) was used for Rosmarinic acid and similar structures, meaning tannin-like structure in the Lamiaceae family. A short time later, in 1958, two Italian chemists isolated Rosmarinic acid from *Rosmarinus officinalis* for the first time and named Rosmarinic acid. The structure is discovered as the 3,4-dihydroxyphenyllactic acid ester of caffeic acid. Biogenetic studies with Rosmarinic acid began in the 1970s. It was found that how Rosmarinic acid was synthesized starting from phenylalanine and tyrosine by radioactive labeling of the amino acids of *Mentha* sp. The caffeic acid moiety consists only of phenylalanine and the 3,4-dihydroxyphenyllactic acid moiety consists only of tyrosine. The biosynthesis pathway has also been confirmed by plant cell culture studies with *Coleus blumei* (Petersen & Simmonds, 2003).

PHYTOCHEMISTRY OF ROSMARINIC ACID

Main Plant Sources Which Contain Rosmarinic Acid

Acanthaceae: *Thunbergia laurifolia*
Apiaceae: *Cuminum cyminum*, *Eryngium alpinum, Sanicula europaea,*
Araceae: *Anthurium versicolor*
Asteraceae: *Artemisia capillaris*, *Baccharis chilco, Calendulla officinalis*
Boraginaceae: *Anchusa azurea, A. officinalis, Arnebia euchroma,A. purpurea, Cordia americana, Echium vulgare, Heliotropium foertherianum, Lithospermum erythrorhizon, Symphytum officinale, Tournefortia sarmentosa*
Cannaceae: *Canna edulis*, *Canna indica*
Lamiaceae: *Agastache rugose, Coleus blumei, Hyptis verticillata, Lavandula angustifolia, Melissa officinalis, Mentha* sp*., Nepeta cadmea, Ocimum basilicum, O. gratissimum, Origanum majorana, O. vulgare, Orthosiphon stamineus, Perilla frutescens, Plectranthus ecklonii*, *Prunella vulgaris,*

Rabdosia rubescens, *Rosmarinus officinalis, Salvia officinalis, S. trichoclada, S. verticillata, S. miltiorrhiza, Satureja parvifolia, Thymus vulgaris,*

Maranthaceae: *Maranta depressa*, *M. leuconeura*

Sterculiaceae: *Helicteres isora*

Zosteraceae: *Zostera noltii* (Kuruuzum-Uz *et al.,* 2004; Kuruuzum-Uz *et al.,* 2010; Demirezer *et al.,* 2012; Demirezer *et al.,* 2015; Petersen, 2013; Yuzbasioglu *et al.,* 2015; Amoah *et al.,* 2016; Al-agawany *et al.,* 2017).

Biotechnological Production

Plant cell cultures allow to obtain Rosmarinic acid at concentrations much higher than that obtained from the plant under certain conditions. The first cell cultures for the production of Rosmarinic acid were made with *Coleus blumei* (Petersen & Simmonds, 2003). Suspension cultures of this species have been found to contain up to 21% of Rosmarinic acid by dry weight. Then, cell cultures were prepared from other plant species to obtain Rosmarinic acid. The highest Rosmarinic acid content was found in the suspension culture of *Salvia officinalis* as 36% of the dry cell weight in low osmolarity medium with 5% sucrose (Park *et al.,* 2008). The effect of the amount of sucrose on the amount of Rosmarinic acid was investigated and in studies with *C. blumei* and it was found that the amount of Rosmarinic acid was proportional to the sucrose level. It has been found that one of the growth-limiting factors is phosphate (Gertlowski *&* Petersen*.,* 1993). In other studies, it was found that the amount of Rosmarinic acid increased with the addition of fungal infection agents (e.g. yeast extract, *Pythium aphanidermatum*) (Szabo *et al.,* 1999)). This study showed that Rosmarinic acid plays a role as a defense component against pathogens and herbivores. Rosmarinic acid has a repellent effect against an insect found in the tobacco plant (tobacco hornworm- *Manduca sexta*). Studies with plant cell cultures, for example *C. blumei*, *Anchusa officinalis* or *Salvia* sp, have yielded much higher amounts of Rosmarinic acid than those from plants (up to 36% of the dry weight). Therefore, the biotechnological production of Rosmarinic acid by plant cell culture is more proposed (Petersen & Simmonds, 2003; Oskay & Oskay, 2009).

Extraction and Isolation

Various methods and techniques used for the extraction and isolation of polyphenols from plant material are also selected techniques for Rosmarinic acid. Amoah *et al*. (2016) and Ngo *et al.* (2018) reviewed and summarized the extraction and isolation studies of Rosmarinic acid in their reviews. It has been used various methods for the extraction of Rosmarinic acid, such as hydro distillation, boiling and maceration, Soxhlet Extraction, Pressurized Liquid Extraction, Ultrasonic-Assisted extraction, Supercritical Fluid Extraction, Microwave Assisted Extraction, Accelerated Solvent Extraction, Heat Reflux Extraction and Enzyme Assisted Extraction. In most of the research, it has been used different polar solvents for extraction such as water, ethanol, methanol, *n*-butanol and isopropyl alcohol. Analytical techniques used to determine and isolation this compound in plant extracts are mainly spectroscopic and chromatographic methods (Liquid-liquid/solid-liquid chromatography). Recently, high-speed countercurrent chromatography which were used led to one-step isolation and purification of this substance with a purity of about 88% from *S. miltiorrhiza*. 1D- and 2D-NMR spectroscopy have been used for elucidation of Rosmarinic acid (Kuruuzum-Uz *et al.,* 2004; Demirezer *et al.,* 2012; Amoah *et al.,* 2016; Akoury, 2017; Ngo *et al.,* 2018).

THE MEDICAL SIGNIFICANCE OF ROSMARINIC ACID

Rosmarinic acid has been found very effective as antioxidant, antipyretic anti-inflammatory, anticancer, antiviral, antimicrobial, antiallergic, immunological, antidiabetic, antidepressant, anti-aging and fertility stimulator through *in vitro* and *in vivo* studies. Rosmarinic acid also has showed photoprotective, hepatoprotective, nephroprotective and cardioprotective effect in many experimental assays. Nevertheless, until now only a few clinical studies with pure Rosmarinic acid has been realized (Bhatt *et al.,* 2013; Friedman, 2015; Amoah *et al*. 2016, Alagawany *et al.,* 2017; Nadeem *et al.,* 2019)

Antioxidant Activity

Rosmarinic acid, a polyphenolic molecule, has antioxidant properties that are primarily related to free radical scavenging, which contributes to membrane stability and protection against oxidative damage. The concentration of lipid peroxidation and Rosmarinic acid has a negative relationship. It provides radical stability by forming intramolecular hydrogen bonds between the free hydrogens of the hydroxyl and phenoxyl radical (Amoah *et al.,* 2016; Alagawany *et al.,* 2017; Cuvelier *et al.,* 1992).

Anti-inflammatory Activity

Anti-inflammatory studies have realized through *in vitro* and *in vivo* studies of various inflammatory diseases like arthritis, colitis, pancreatitis, mastitis, periodontal diseases, neurits, allergic rhinitis, asthma and atopic dermatitis on Rosmarinic acid. Inflammatory illnesses are characterized by an imbalance of inflammatory mediators and cells and are caused by excessive immunological responses. It affects many factors such as chemotaxis, neutrophil activation, histamine release, and prostacyclin biosynthesis in inflammation. It has been reported that, unlike NSAIDs and glucocorticoids and other modulators of complement activation, Rosmarinic acid does not interfere with cyclooxygenase activity and inhibits prostanoid release at the site of inflammation where complement activation occurs. Since it does not interfere with cyclooxygenase activity, side effects are less. Luo *et al*. (2020) reviewed deeply the important role of Rosmarinic acid in treating inflammatory diseases through multiple mechanisms. These studies showed that it has good effect in various inflammatory diseases (Rampart *et al.,* 1986; Englberger *et al.,* 1988; Nadeem *et al.,* 2019; Luo *et al.,* 2020).

In a clinically study investigated the effect of Rosmarinic acid on atopic dermatitis, one of the inflammatory diseases of the skin, 21 patients with atopic dermatitis were used. According to the local severity scoring of the atopic dermatitis index, erythema in the antecubital fossa decreased significantly. The water loss of the transepidermal antecubital fossa was significantly reduced at 8 weeks compared to pretreatment. According to the results obtained from the questionnaires, dryness, rash and general atopic dermatitis symptoms improved. Through *in vivo* experiments, he demonstrated the possible clinical use of Rosmarinic acid as a therapeutic agent for atopic dermatitis (Lee *et al.,* 2008).

Immunological Activity

Rosmarinic acid has also been demonstrated to decrease immunoglobulin responses and inflammatory responses in polymorphonuclear leukocytes, which could explain its success in human clinical trials for

treating seasonal allergy rhinoconjunctivitis. Rosmarinic acid's anti-inflammatory and immunomodulatory properties may make it a promising new therapeutic option for auto-immune illnesses (Friedman, 2015).

Antiallergic Activity

Allergic rhinitis is characterized by an allergic reaction. The early stage is characterized by sneezing, epistaxis, and pruritus, mediated by histamine, prostaglandins, leukotrienes, and cytokines, including the activation of immunoglobulin E-dependent, mast cells and basophils and production of inflammatory mediators. The late stage is characterized by the accumulation of mast cells, eozonophils and basophils in the epithelium. To maintain the allergic response, eozonophiles, basophils, T cells, histamine, leukotrienes, proinflammatory cytokines, cyclooxygenase-2 and chemokines act together. Results of assays demonstrated that the anti-inflammatory and immunological effects of Rosmarinic acid are similar in animals and humans. It has been found that Rosmarinic acid is a safe and feasible treatment option for seasonal allergic rhinoconjunctivitis (Takano *et al.,* 2004; Fkui *et al.,* 2009; Nadeem *et al.,* 2019).

Antimicrobial Activity

Rosmarinic acid has a noticeable antibacterial effect against *Bacillus subtilis, Micrococcus luteus* and *Escherichia coli*. When given topically in an *in vivo* model, Rosmarinic acid is efficient in lowering gingival inflammation and plaque accumulation as an antioxidant and anti-inflammatory molecule. Because of its antibacterial properties and helps to lower inflammation, rosmarinic acid is beneficial for topical skin infections of the epidermis and oral mucosa (Bhatt *et al.,* 2013; Alagawany *et al.,* 2017).

Antiviral Activity

Flaviviruses are common human pathogens that can cause something from a slight fever to severe encephalitis. Japanese encephalitis virus (JEV) is one of them, and it attacks the central nervous system, causing acute encephalopathy in children. It was founded that Rosmarinic acid was discovered to lower levels of proinflammatory cytokines and chemokines in the study using a mouse model. In the JEV-infected group, the incidence of microglia in the brain was 30 times higher than in the Rosmarinic acid-treated group. The expression of viral proteins and the transcription of mRNA were both considerably decreased by Rosmarinic acid. As a result, rosmarinic acid is recommended as a promising candidate for reducing the neurological problems seen in JE patients (Swarup *et al.,* 2007).

Effect on Neurodegenerative Diseases

Several studies have suggested that oxidative stress may play a role in Alzheimer's disease etiology. Lesions related with free radical exposure are common in Alzheimer's patients' brains. Superoxide dismutase (SOD), glutathione peroxidase (GPx), and ascorbate reactive oxygen species (ROS) are antioxidant molecules present naturally in the human body that may scavenge free radicals. According to a study, Rosmarinic acid increased the total lifespan of ALS model mice and successfully reduced the motor function impairment caused by the disease progression. It has also been discovered to help with motor neuron degeneration. By suppressing pyrrolyl oligopeptidase, rosmarinic acid can boost cogni-

tion. According to the findings, subchronic treatment of Rosmarinic acid for 2-3 weeks improved spatial memory. (Bhatt *et al.,* 2013; Friedman, 2015).

Antidepressant Activity

Rosmarinic acid has been discovered to have a significant antidepressant effect in a single dose by suppressing histamine release from mast cells. While inhibiting nitric oxide generation and release, rosmarinic acid stimulates the 1-adrenoreceptor. Because of its influence on the brain's adrenoreceptor systems, it has been theorized that it could help with stress and depression treatment. In the swim test, it was discovered that it inhibited the generation and release of histamine in mice. In a swim test, mice were given rosmarinic acid intraperitoneally, and it was discovered that it greatly reduced immobility time. Other than inhibition of monoamine transporters and monoamine oxidase, rosmarinic acid may also have antidepressant-like properties such as induced cell proliferation could be one of them (Bhatt *et al.,*2013).

Anticancer Activity

The anticancer effect of RA has been related to a number of pathways (Bhatt *et al.,* 2013). Rosmarinic acid was investigated for its chemical inhibitory capacity against the colon carcinogen 1,2-dimethylhydrazine (DMH), malignancies, lipid peroxidative products, and cell proliferative and apoptotic proteins. It was discovered that giving treated rats Rosmarinic acid protected them against the inhibitory effects of DMH, suggesting that Rosmarinic acid may be employed as a chemical preservative. When comparing animals treated with different amounts of Rosmarinic acid to negative controls, mutagenicity tests revealed no increase in micronucleus frequency. Rosmarinic acid is considered to suppress the degradation of biochemical indicators (lipid peroxidation, antioxidant and detoxification enzymes), as well as p53 and Bcl-2 proteins, in 7,12-dimethylbenzanthracene (DMBA)-induced oral carcinogenesis. In the rat, RA administration inhibited tumor development and proliferation in 1,2-dimethyldrazin-stimulated colon carcinogenesis. TNF, COX-2, and IL-6 levels were all reduced by RA administration, and p65 expression was regulated. The effects of RA on cell cycle arrest and death in prostate cancer cell lines were mediated by changes in the levels of histone deacetylases (Alagawany *et al.,* 2017; Bhatt *et al.,* 2013; Hossan *et al.,* 2014).

Angiogenesis Inhibitory Activity

Rosmarinic acid has been reported to suppress essential processes of angiogenesis in human umbilical cord endothelial cells, such as proliferation, migration, adhesion, and tubing, in a concentration-dependent manner. In addition, RA has been shown to lower intracellular reactive oxygen species, hydrogen peroxide-dependent VEGF production, and endothelial cell IL-8 release (Bhatt *et al.,* 2013).

Antidiabetic Activity

Much research has been performed on the anti-diabetic activity of Rosmarinic acid based on *in vitro* assays and *in vivo* studies. In the results, it was found that pancreatic amylase activity decreased at varying rates depending on the Rosmarinic acid content of the extract. It was found that Rosmarinic acid inhibited

protein and/or enzymes due to its phenolic structure. Natural alpha-amylase inhibitors from herbal sources containing Rosmarinic acid may offer an attractive therapeutic approach in the treatment of hyperglycemia by reducing starch glucose secretion and have the potential to be used in the treatment of type 2 diabetes mellitus and obesity (McCue & Shetty, 2004). By regulating antioxidant enzymes and attenuating the numbers of pro-inflammatory T helper 2 and T regulatory cells, RA prevented the incidence of diabetes and preserved normal insulin secretion, ROS, and reactive nitrogen species (RNS). Dipeptidyl peptidase IV (DPP-IV) and protein tyrosine phosphatase 1B were also inhibited with rosmarinic acid. Rosmarinic acid was found to regulate glucose absorption in a considerable way. *In vivo* investigations revealed that oral therapy with Rosmarinic acid repaired blood glucose levels and regulated circulating adipokines in diabetic rats, as well as alleviating the hypoglycemia effect of streptozocin-induced type 1-like diabetic rats in a dose-dependent manner. Rosmarinic acid's considerable antioxidant properties may also protect against diabetic glomerular degeneration and nephropathy (Nadeem *et al.,* 2019)

Effect on Sexual Behavior in Mice with Diabetes

Reproductive problems, infertility, and diminished libido are just a few of the problems that diabetes can cause. Antioxidants are crucial in the etiology of chronic diabetes mellitus because they reduce oxidative stress. The level of sexual behavior in the groups receiving Rosmarinic acid was shown to be considerably higher. Rosmarinic acid has enhanced serum testosterone levels as well as ejaculation, libido, and sexual activity in all groups, according to the findings. This compound protects against diabetes-related adverse effects by increasing serum testosterone levels. In rats, therapy with rosmarinic acid had a considerable preventative and curative effect on diabetic disease (Farzadi *et al.,* 2011).

Photoprotective Activity

UVA radiation causes the production of reactive oxygen species (ROS) in exposed cells, resulting in oxidative stress, which causes significant cell damage and cell death via apoptosis or necrosis. In one study, Rosmarinic acid was tested for its ability to protect human keratinocyte cell lines from UVA-induced alterations. Rosmarinic acid was found to be effective in reducing UVA-induced cell viability. Rosmarinic acid was discovered to prevent intracellular lipid peroxidation and limit UVA-induced ROS generation. DNA damage was dramatically reduced after the administration of Rosmarinic acid. In addition, treatment with Rosmarinic acid reduced UVA-induced caspase-3 activation. According to the findings, Rosmarinic acid can be used in skincare products to protect against UVA-induced oxidative stress (Psotova *et al.,* 2015). UV, sun, and other ionizing radiations disrupt skin homeostasis by causing reactive oxygen species and cellular DNA damage. Moreover, rosmarinic acid by modulating tyrosinase activity and increasing melanin formation acts as a free radical scavenger and inducer of the body's own endogenous defense mechanisms (Psotova *et al.,* 2006; Bhatt *et al.,* 2013).

Metabolism and Pharmacokinetic Properties

Pharmacokinetics was initially researched in animal models, but various human investigations were also undertaken. This substance can be used topically, pulmonary, intranasally and intravenously. Per oral application, on the other hand, is the most common route of entry into the human body. It's likely that the gut microflora metabolizes it primarily, providing simple, more easily absorbed phenolic units. The

Rosmarinic acid molecule undergoes structural modifications as well as conjugation reactions inside the body. Renal excretion is the primary route of elimination. The major metabolites identified in urine are Rosmarinic acid sulfoglucuronide conjugates and methyl Rosmarinic acid sulfoglucuronide conjugates, implying that polyphenolic compounds are conjugated via glucuronidation and/or sulfation in organs like the gut and liver. Metabolism studies have shown that Rosmarinic acid is rapidly absorbed, then methylated, and subsequently excreted in the urine. The majority of Rosmarinic acid and its metabolites are found in the plasma in conjugated form. The major metabolites found in urine are sulfoglucuronide conjugates of Rosmarinic acid and methyl Rosmarinic acid, suggesting that conjugation of polyphenolic compounds occurs by glucuronidation and/or sulfation in tissues such as the intestine and liver (Amoah *et al.,* 2016). Up to 75% of Rosmarinic acid and its metabolites are excreted within the first 6 hours after ingestion (Baba *et al.,* 2005). Recently, to improve the bioavailability of Rosmarinic acid, nanoparticle-based RAs were studied to bypass gastric degradation (Madureira *et al.,* 2016) and chitosan-based nanoparticle delivery was also evaluated for ocular delivery (da Silva *et al.,* 2016). Future studies could focus on pharmaceutical formulations that inhibit RA from metabolizing quickly and allowing it to penetrate into different parts of the human body (Hitl *et al.,* 2021).

Safety

Rosmarinic acid has an LD_{50} of 561 mg/kg in mice, indicating that it is quite low in toxicity. After the injection of hepatoxin carbontetrachloride, Rosmarinic acid was given orally. It was discovered that Rosmarinic acid had no effect on the weight of the animals' livers or their ALT levels. The histopathological and serum markers of study-induced liver injury were improved by Rosmarinic acid. The ADI (acceptable daily intake) value was calculated as 500 mg per day (Friedman, 2015).

CONCLUSION

The majority of present-day drugs have been produced from natural compounds. It has been scientifically studied potential use for wellness in about 10% of 250,000 species of plants estimated worldwide (Cragg & Newman, 2002). The increasing role of natural compounds in drug development has been, not only belong to their direct usage as medicine but also can be a model for new drug synthesis. Rosmarinic acid is a phenolic compound that is mostly found in the families of Lamiaceae and Boraginaceae, but has a wide distribution in various families. It is found in rosemary, thyme and sage species, which are frequently used as spices and tea. Since Rosmarinic acid is found in spices that we use frequently in our daily lives, it is easily obtainable and accessible. *In vitro* cultured plant cells can produce large amounts of RA, allowing for cost-effective commercialization.

The use of herbal products has brought the use of herbal products to the agenda, as it has been reported that synthetic antioxidants may have toxic effects on human health, and therefore, the restriction or prohibition of their use has brought about the preference of natural products by conscious consumers. In recent years, studies on the use of medicinal and aromatic plants such as sage, thyme and rosemary, which are rich in phenolic compounds, as preservatives in foods have gained momentum. It has been found that Rosmarinic acid, which is common in these species, has a strong antioxidant effect. Rosmarinic acid provides radical stability by forming intramolecular hydrogen bonds between the free hydrogens of the hydroxyl and phenoxyl radical. Studies on Rosmarinic acid mostly focused on its antioxidant ef-

fect. As a result of studies for its anti-inflammatory effect, it has been reported that Rosmarinic acid, unlike NSAIDs, glucocorticoids and other modulators, does not interfere with cyclooxygenase activity and inhibits prostanoid release in the inflammatory region where complement activation occurs. It has been discovered that since it does not interfere with the cyclooxygenase activity, the side effects will be less so it can have an important use for anti-inflammatory purposes. In recent years, important studies have been carried out especially for neurodegenerative diseases and the mechanism of these diseases has been tried to be clarified. Since the possibility of the free radical formation may be at the root of these diseases, it has been found that Rosmarinic acid alleviates the degeneration of motor neurons, especially in studies conducted for Alzheimer's and ALS diseases. With these studies, it has been realized that Rosmarinic acid is one of the important molecules that can provide additional benefit to the treatment that provides a neuroprotective effect. In addition to *in vitro* studies, clinical investigations suggested its benefits in dermatological, allergic, and osteoarthritic disorders, as well as for improving cognitive performance and in metabolic syndrome treatment. Early treatment with Rosmarinic acid may help to prevent the development of diabetes.

It was found that Rosmarinic acid reached a maximum concentration in plasma after 0.5 hours, followed by a gradual increase in the plasma concentration of methyl-Rosmarinic acid, reaching a peak at 2 hours. It was later found that approximately 75% of the total metabolites were excreted in the urine within 6 hours. In clinical studies, no abnormalities were observed in whole blood cell counts, hepatic and renal function tests and blood tests including total protein, electrolytes, lipids, uric acid and creatine phosphokinase at doses up to 500 mg/day of Rosmarinic acid. It has been found that Rosmarinic acid is suitable for daily use. Rosmarinic acid is a sufficient amount in many plants used as spices in the world, and besides its antioxidant effect, it has a protective effect for cancer and neurodegenerative diseases, which are important problems today. Due to its very low toxicity. The investigations have mainly addressed Rosmarinic acid sources, Rosmarinic acid production and the physiological and pharmacological effects of Rosmarinic acid. The effect of Rosmarinic acid has been studied in animal experiments and clinical trials in the field of antioxidant, anti-inflammatory, antiviral, anticancer, antiallergic, photoreactive effects and neuroprotective effects, etc. Studies on its effects on physiological and pathological conditions and possible protective effects on diseases are still ongoing.

More clinical trials are necessary to know about the safety and efficacy of Rosmarinic acid in the treatment of illnesses. It is important to evaluate the pre-clinical and clinical studies on Rosmarinic acid together, to eliminate the deficiencies, to encourage its industrial production and use in various fields beneficial for human health. Future studies should investigate the kinetics during long-term application in patients who would have potential benefits from RA usage. These works could focus on pharmaceutical formulations that inhibit RA from metabolizing quickly and allowing it to penetrate into different parts of the human body.

There are still interesting aspects to this molecule, such as its biotechnological production, biological activities and its presence in the plant kingdom.

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Chapter 16
The Importance of Arugula (*Eruca sativa*) and Pharmacological Effects of Different Phytochemical Components in Its Content for Human Health

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ABSTRACT

Rocket salad (Eruca sativa), a member of the Brassicaceae family, is an important vegetable for human health because of its antioxidant, anti-inflammatory, anticancer, antiproliferative, and antiangiogenesis properties, as well as its rich chemical composition. Important phytochemical substances in rocket salad, including flavonoids and glucosinolates, have an important function in human health protection. These components can scavenge free radicals, reduce lipid peroxidation, and have anticancer effects by activating apoptosis in cancer cells. As a result, in terms of defending human health, it is believed that the consumption of this vegetable has a significant role in protecting against diseases caused by numerous factors and in the healthy functioning of the body's immune system.

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INTRODUCTION

Arugula salad, also known as arugula, is a very important plant in terms of human health and belongs to the *Brassicaceae* family, which is characterized by its unique leaves. Species belonging to the genus *Eruca and Diplotaxis* are considered arugula. Arugula, also called *Eruca sativa*, is found in different parts of the world and is known as the most consumed type (Tripodi *et al.,* 2017). A significant part of the different phytochemicals in arugula consists of different components such as flavonoids, phenolic components, glucosinolate, vitamin C and carotenoids. These components in the content of arugula are responsible for different pharmacological activities such as antioxidant, cytoprotective, anticancer, anti-ulcer, diuretic, hepatoprotective activity (Sjaafar & Sjaafar, 2019). Although the flavonoids contained in arugula *(Eruca sativa)* include kaemferol, isorhamnetin, rhamnocitrine, quercetin, and their glycosides, the effective properties of these components such as free radical scavenger, lipid peroxidation inhibitor, enzymatic activity modulation are of great importance for the protection of human health (Hetta *et al.,* 2017; Cuellar *et al.,* 2021).

This chapter is aimed to give general information about arugula, which has various biological activities with its important biochemical components in terms of human health, whose importance is increasingly understood in this respect, and how the general mechanism of action of arugula in humans is in terms of health and how it shows this effect. In addition, it is aimed to enlighten the subject by evaluating the studies that have been done in this field in recent years.

BACKGROUND

Definition and Types of Arugula

Arugula, a plant in the Brassicaceae (cruciferous) family native to the regions surrounding the Mediterranean Sea, *Eruca Sativa* (Garden arugula) (Figure 29.1), *Diplotaxis muralis* (one-year wall arugula) (Figure 29.2), *L. Diplotaxis tenuifolia* (perennial wall arugula), true rocket, rocket salad, rocket It is also known as rocket, white pepper. *D. Tenuifolio*, which grows in Europe and Australia, is the more dominant and common genus. Today, varieties of arugula are grown commercially in various countries such as the USA, England, Italy, Spain, Morocco, Israel, India, and Australia (Gajra & Vinay, 2014).

"Arugula" is distinguished from each other by the sharp flavors of the leaves of its different species. Mildly flavored varieties of *Eruca vesicaria* (L.) Cav is consumed as a vegetable in the Middle East. *Eruca v.* is a polymorphic species traditionally consumed in central and southern Italy. *Diplotaxis tenuifolia* is a wild herb popularly consumed in Italy, Portugal, and France. Beginning in the 1970s, with the increase in knowledge about this species, it has been domesticated (Pasini *et al.,* 2011). Five different genotypes and phenotype characteristics of *Diplotaxis tenuifolia and Eruca vesicaria* are shown in Table 29.1.

Eruca sativa species have white flowers, lobular-shaped leaves and grow naturally as a weed in corn and flax fields, waste dumps, and roadsides. *D. tenuifolia* naturally grows in sandy and calcareous soils, roadsides, neglected areas, and rock cracks. It has yellow flowers and serrated leaves. Wild arugula, successfully grown in unimproved environments, is a halophyte plant and can be used in saline agriculture. *E. sativa* and *D. tenuifolia* species, which are generally characterized by the strong taste of their edible leaves, differ in leaf morphology and seed size, carbon fixation system, glucosinolate (GSL) content, growth rate (Cavaiuolo & Ferrante, 2014).

Table 1. Arugula genotype examples

Codes	Genotype	Homeland	Features
G1	*Diplotax tenuifolia (Dragon Tongue)*	France	Red-veined leaves
G2	*Diplotax tenuifolia (var. Frastagliata)*	İtaly	Rough leaves
G3	*Diplotax tenuifolia (var. Capriccio)*	İtaly	İndented leaves
G4	*Eruca sativa (cropped)*	Italy	Broad Leaves
G5	*Diplotax tenuifolia (Foglia d'olivo)*	Italy	Long narrow leaves with slightly jagged margins
G6	*Diplotax tenuifolia (Piccante)*	United States	Dark green, serrated leaves

(Petretto et al., 2019).

Historical research shows that arugula is used both as a garden herb and as a spice. According to the 2010 data of the Turkish Statistical Foundation (TUIK), arugula is consumed raw in salads or cooked in various dishes. It is reported that the annual production in Turkey reaches 4058 tons (Barlas *et al.,* 2011).

Arugula plant reaches a production of 12.93 tons with a production area of 10.38 thousand decares in Turkey. 2.55% of the total production area is rocket cultivation and 1.69% of the production amount is made in Antalya. The production period in rocket cultivation is 1-1.5 takes months (Gözükara *et al.,* 2019).

Structure, Function, and Cultivation of Arugula

Glucosinolates in the structure of the *Brassicaceae* family react with myrosinase enzymes (thioglucoside glucohydrolase, EC 3.2.1.147) to form several classes of compounds with potential benefits to human health. Arugula species are known to have high concentrations of glucosinolate, carotenoids, fibers, vitamin C, and flavonols. The flavonoids found in arugula are phenylpropanoids conjugated with sugar. (C6 − C3 − C6) Isothiocyanates (ITCs), thiocyanates, nitriles, and sulfates are chemical compounds effective in the formation of the sense of taste. The ITCs in arugula may taste bitter due to thiourea, such as 6-n-propylthiouracil (used to produce synthetic bitterness). ITCs are also known to contribute to temperature and burning perceptions on the tongue. In a study, chemicals such as glucosinolate (GSL), progoitrin/epiprogoitrin, and dimeric-mercaptobutyl glucosinolate (DMB) were found in arugula were found to be associated with the bitter taste and the sharpness of perceived bitterness (Bell *et al.,* 2015; Bell *et al.,* 2017). ITCs are considered potent inducers of phase II enzymes (e.g., glutathione transferases, NAD(P)H: quinone reductase, epoxide hydrolase, etc.) important in detoxifying electrophiles and protecting against oxidative stress. The main glucosinate (GL) found in arugula seeds is glucoerucine (GER), which represents 95% of the total GLs (+108 ± 5 μmol g-1 d.w.) (Barillari *et al.,* 2005).

Studies show that the highest glucosinate content is obtained from arugula plants grown in the warmer months. A fertilizer high in nitrate-nitrogen increases the leaf color, vitamin C, and nitrate content, while the use of farm fertilizer increases the total glucosinate content. The quality of arugula (leaves shrinkage and rancidity) at low and high temperatures, in addition, different fertilizers and various growing media are effective on the yield and composition of the rocket plant (Taherlou, 2011).

Arugula grown in soil contains approximately 7000-8000 mg kg^{-1} (ppm) high levels of nitrate, and this value can exceed 9000 ppm in winter (Ferrante *et al.,* 2003). However, nitrate reduction products are toxic and can cause serious pathologies in humans. Italy imposes strict provisions on the import and

Figure 1. Eruca vesicaria sativa (garden arugula)

export of arugula, as well as lettuce, spinach, and potatoes. The nitrate content in fresh arugula should not exceed 2.5-4.0 g kg (Santamaria *et al.,* 2002).

There are many factors affecting the mineral and vitamin content of the plants, such as the quality of the seed used, the suitability of the planted soil, and the fertilizer used. In addition to ensuring the correct use, storage, and storage conditions of the harvested product, attention should be paid to the products used in cleaning. The disinfectants used cause vitamin C loss in arugula (Ağagündüz & Karabudak, 2017).

Diplotaxis tenuifolia and other leafy vegetables are subjected to multiple stresses during harvest, including mechanical damage, improper temperature storage or transportation, and low light. It is thought that these stress factors affect the decay rate and shelf life of the product after harvest (Spadafora *et al.,* 2019).

It has been observed that rockets grown under plastic with 27% UV-B permeability in greenhouse cultivation have much higher luteolin and quercetin contents compared to rockets grown under UV-B radiation blocking film (Mormile *et al.,* 2019).

The main and side-chain chemical structures of glucosinolate compounds found in arugula were illustrated in Figure 3. The main glucosinolate (GLS) in the leaves of *Eruca sativa* L. (salad arugula) is defined as 4-mercaptobutyl GLS. 4-methylthiobutyl GLS and 4-methyl-sulfinyl butyl GLS are found in lower concentrations (Bennett *et al.,* 2002). Researchers identified more than 50 flavonoid compounds in four different types of arugulas. While wild arugula contains quercetin (43.5 mg/ 100 g), salad arugula

Figure 2. Diplotaxis muralis

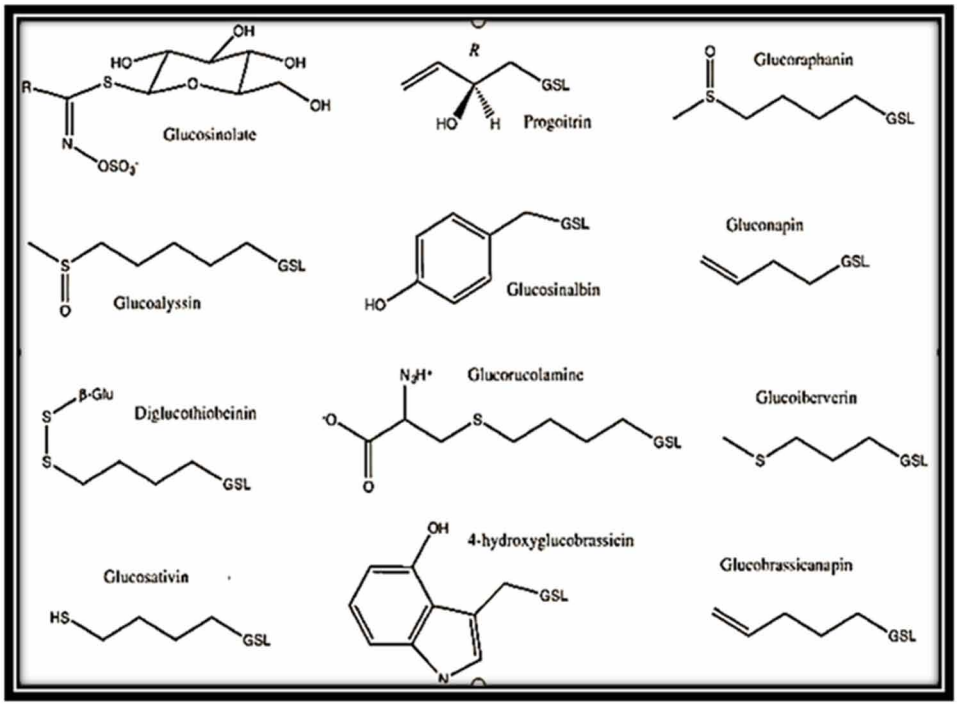
mostly contains kaempferol-3,4¢-glucosyl (97.8 mg). *Eruca* species accumulate kaempferol derivatives in their tissues, while *D. tenuifolia* predominantly accumulates quercetin instead (Martinez-Sanchez *et al.,* 2008). Such core aglycones are kaempferol, quercetin, and isorhamnetin; Table 2 contains an up-to-date list of all flavonol compounds identified in arugula (Bell & Wagstaff, 2014).

EFFECTS OF ARUGULA ON HEALTH

In addition to its use in nutrition, arugula is also used in the health and cosmetic industries due to its phytochemical activity in our country. It has a wind rage of different utilization in the pharmaceutical industry due to its anti-bleeding, depurative, antiphlogistic, diuretic, digestive, pain-reducing, stimulating, and laxative effects (Uyar *et al.,* 2013).

Important isothiocyanates, such as the sulfur compounds in the structure of arugula, can inhibit oxidative stress and change cytokine activity, as well as various biological factors that are of great importance for the control of human health, such as stopping angiogenesis and cell cycle progression,

Figure 3. Main and side-chain chemical structures of glucosinolate compounds found in arugula (Bell & Wagstaff, 2019).



stimulating apoptosis, lowering blood pressure, having cardioprotective effects and antiviral effects (Sanlıer & Güler, 2018).

Erucin, one of the important isothiocyanates in arugula, has antihypertensive, antiadipogenic, and anti-inflammatory effects as well as inhibiting the proliferation of cancer cells (Melchini *et al.,* 2009; Chae *et al.,* 2015; Martelli *et al.,* 2020; Martelli *et al.,* 2021). Arugula also has effects such as tumorigenesis inhibition and hepatoprotective (Durazzo *et al.,* 2013). Heat treatment destroys both myrosinase and glucosinolates. For this reason, it is recommended to consume arugula raw to benefit from its cancer-protective effects (Nugrahedi *et al.,* 2015).

The importance of arugula on human health is provided by its ability to inhibit the accumulation of free radicals, which cause certain damage over time in body cells and tissues. The physiological effects of phenolic compounds and flavonoids in arugula are due to the free radical scavenging, metal chelating activity, and electron/hy, hydrogen transfer of these components (Balasundram *et al.,* 2006; Dai & Mumper 2010; Fratianni *et al.,* 2014). Arugula is a vegetable with a high potential for disease prevention because of its components such as calcium, magnesium, potassium, folate, vitamin c, vitamin k, iron, glycoisocyanates, flavonoids, and carotenoids, as well as a wide range of biological activities (Figure 4).

Although there are many studies conducted in recent years on the effects of arugula on health, studies on the evaluation of different components of arugula in terms of biological and pharmacological activity are also continuing.

In a study comparing arugula grown in Bulgaria and Italy in terms of phenolic content, antioxidant activity, and hydroxycinnamic acid derivatives, it was found that phenolic content was higher in Bul-

Table 2. Flavonoid compounds are found in arugula

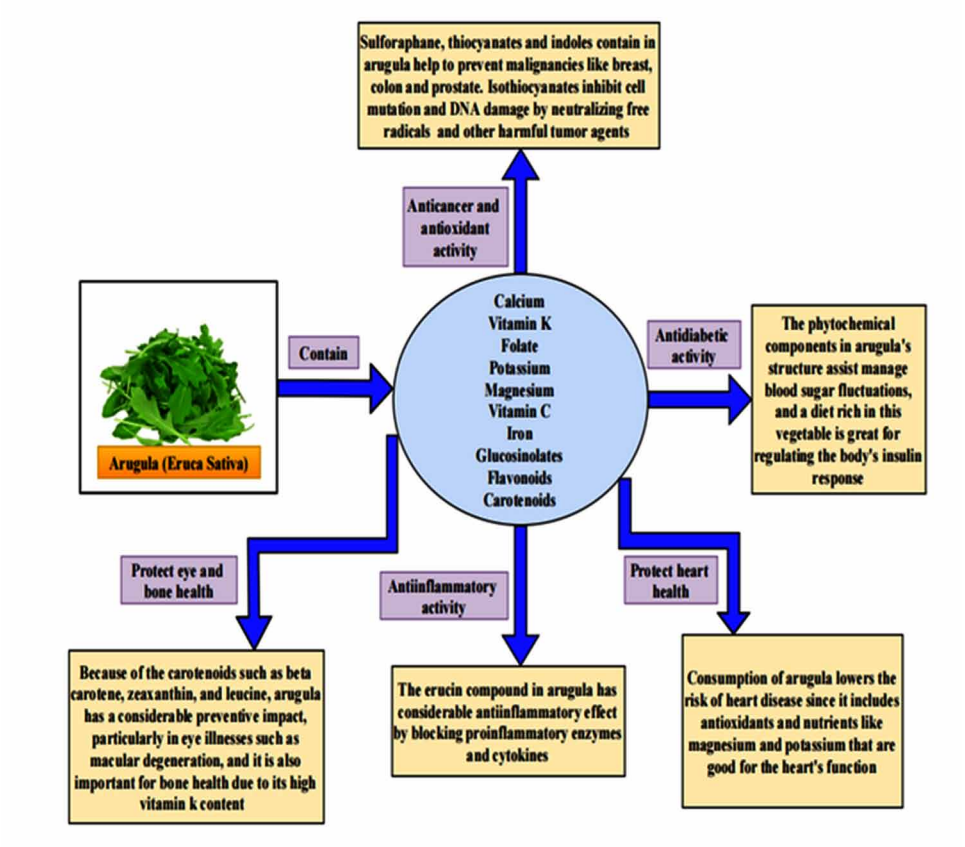
Flavonoid compounds	*Eruca*	*Diplotaxis*
I 3,4¢-disc	X	X
I 3-Glc	X	
K 3-(2-Sep-Glc)-4¢-Glc	X	
K 3,4¢-disc K 3-Glc	X	X
Q 3-Glc K 3-diGlc-7-Glc K 3-Sinp-triGlc-7-Glc Q 3,4¢-diGlc-3¢-(6-Caf-Glc)	X	
	X	
M	X	
Q	X	
R	X	
Q 3-(2-Caf-Glc)-3¢-(6-Sep-Glc)-4¢-Glc		X
Q 3-(2-Mcf-Glc)-3¢-(6-Sep-Glc)-4¢-Glc Q 3-(2-Fer-Glc)-3¢-(6-Fer-Glc)-4¢-Glc Q 3-(2-Fer-Glc)-3¢-(6-Sinp-Glc)-4¢-Glc Q 3-(2-Sinp-Glc)-3¢-(6-Sinp-Glc)-4¢-Glc Q 3,3¢,4-triGlc Q 3,4¢-diGlc-3¢-(6-Fer-Glc) Q 3,4¢-diGlc-3¢-(6-Mcaf-Glc) Q 3,4¢-diGlc-3¢-(6-p Coum-Glc) Q 3,4¢-diGlc-3¢-(6-Sinap-Glc)		X X X X X X X X X X

(Uyar *et al.,* 2013).

garian arugula (4,45 mg gallic acid/g dry weight, hydroxycinnamic acid content was higher in Italian arugula.) as 1.52 mg of chlorogenic acid/g dry weight) (Matev *et al.,* 2018). In a study examining the antitumor and antioxidant activity of arugula (*E. sativa*) in the Ehrlich ascites carcinoma (EAC) tumor model in mice, it was reported that arugula supplementation significantly reduced the tumor volume and weight by showing an antitumor effect in mice bearing tumors, however, it was observed that the lifespan of mice bearing tumors was prolonged. It has been stated that its effect may be due to its high phenolic component content (Elsadek *et al.,* 2021).

In a study examining the antithrombotic activity of the aqueous extract of arugula, it was shown that this extract inhibited the release of platelet inflammatory mediators induced by ADP through inhibition of the NF-kB pathway and had significant antithrombotic activity (Fuentes *et al.,* 2014). In a study examining the effect of hydroethanolic extract of arugula (*E. sativa*) seed extract (ESS) on oxidative stress in rat testis induced by acrylamide (ACR), this extract, especially at a dose of 200 mg/kg, also showed that acrylamide formed in rat testicular cells with the effect of phenolic components and flavonoids in the arugula content. It has been reported that it has a high antioxidant effect against toxic effects and inhibits lipid peroxidation (Abd-Elsalam *et al.,* 2021). In a study in which ultrasonic arugula (*E. sativa*) ethanolic extract was compared with the extract obtained by the maceration method in terms of anticancer, antioxidant, and antimicrobial activity, it was determined that both extracts were

Figure 4. Comprehensive overview of the effect of Arugula and different compounds in its content in protecting human health (Zhang, 2004; Villatoro-Pulido et al., 2012; Bansal et al., 2015; Cho et al., 2013; Fusaro et al., 2017; Tang et al., 2017).



affected by the effect of important bioactive components in the structures of hepatocellular cancer and colorectal cancer cell lines (HepG2 and HT29). It has been reported that these extracts also have antimicrobial and antioxidant activity (Ahmad & Shehta, 2020). In a study examining the metabolic effects of an extract from Arugula (*Eruca sativa* Mill) in an experimental obesity model, rats fed a standard diet and an *Eruca sativa*-supplemented diet for 10 weeks, fed an *Eruca sativa*-supplemented high-fat diet, demonstrated that this diet's adipocyte metabolism and citrate It was concluded that it is effective in regulating synthase activity and reducing triglyceride levels. However, it has been reported that *Eruca sativa* extract prevents body weight gain and improves glucose homeostasis in an experimental obesity model (Piragine *et al.,* 2021). In a study evaluating the anti-inflammatory potential of arugula (*Eruca sativa*) seed extract (ESE), it was determined that ESE could induce anti-inflammatory and neuroprotective effects in NSC-34 motor neurons exposed to the culture medium of LPS-stimulated RAW 264.7 macrophages. It has been reported that *Eruca sativa* exerts this effect by inhibiting inflammatory pathways such as COX2, TLR4, NLRP3, and by limiting proinflammatory cytokine production (Gugliandolo *et al.,* 2018). In a study examining the protective effect of reducing (ER), a phytochemical compound in arugula, against prostate cancer, using prostate adenocarcinoma cells (PC3), it was determined that ER

increased p21 protein expression and ERK1/2 phosphorylation, thus inhibiting PC3 cell proliferation. It was concluded that erucin modulates the molecular mechanisms affecting cancer cell proliferation (Melchini *et al.,* 2013). In a study examining the biochemical effects of the aqueous extract of *Eruca sativa* leaves on the lipid profile and minerals (calcium, magnesium) in the blood of male albino mice, *E. Sativa* increased HDL, decreased cholesterol, triglyceride, and LDL levels, and increased calcium and magnesium levels in mice. It was concluded that it had a positive effect in terms of lipid profile and mineral level (Weli *et al.,* 2021). In a study investigating the effect of ethanolic extract of *Eruca sativa* seed oil on mammary gland cancer cells induced by dimethylbenz(a)anthracene (DMBA) in rats, it was found that this extract inhibited lipid peroxidation, inflammation, and cell proliferation in rat mammary tissue with the effect of flavonoids in its structure, as well as tumor volume. It has been determined that it also provides a decrease in the incidence of tumors (Abdel Rahman *et al.,* 2015).

Arugula's pharmacological and biological properties, as well as the various phytochemical components it contains, are used in a variety of disciplines, particularly in the health sector. If we look at some of these developed products, we can observe that arugula oil obtained from arugula seeds has a favorable effect in the treatment of dry, damaged, and dandruff hair, as well as in decreasing hair loss due to its high antioxidant content. Various products on the market are manufactured in the form of arugula powder as a food supplement and known as arugula extract, which can also be in tablet form. These products help to boost the body's immune system, prevent cardiovascular disease by lowering blood pressure, reducing chronic inflammation, and inhibiting cancer formation. There are also commercially available forms of arugula in the form of tablets produced to reduce andropause symptoms in men and used in this way. In the food industry, it can be produced as arugula cream to be used as an appetizer alongside pasta, fish, and meat.

In a recent study, the napin protein extracted from *Eruca sativa* seeds displayed a cytotoxic effect against Huh7 cells at 25 and 50 μM Napin concentrations, cancer cells were significantly destroyed, and the IC50 was determined by nonlinear regression at 20.49 μM. According to the researchers, the napin protein obtained from *Eruca sativa* may be a possible candidate for the creation and manufacture of an anticancer medicine, and the structural information of these proteins can pave the way for the identification of new anticancer drugs (Khaliq *et al.,* 2021).

In a different study, researchers investigated the effect of glucoerucine in *Eruca sativa* on diabetic neuropathic pain generated by streptozotocin (STZ) in mice, it has been determined that this component can act as a pain reliever due to the phenolic components and glucosinolate in its content (Lucarini *et al.,* 2019).

CONCLUSION

Consumption of vegetables rich in glucosinolates, flavonols, and carotenoid content such as arugula has a significant role in the reduction of cancer risk, improvement of cardiovascular diseases, healing of various ailments related to oxidative stress and inflammation. In *in vitro* and *in vivo* studies, it has been shown that flavonoids, isothiocyanates, and indoles in the arugula have very important roles in terms of human health. It is thought that these components provide this with their effects such as modulation of phase 1 and phase 2 detoxification pathway enzymes, control of cell growth, regulation of cell cycle arrest, induction of apoptosis, and inhibition of angiogenesis by showing the antiangiogenic activity.

Therefore, arugula has a high potential for developing novel drugs, functional food products or dietary supplements.

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Chapter 17
Overview of Extraction, Isolation, and Bioavailability Enhancement of Resveratrol: Phytochemistry and Bioavailability of Resveratrol

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ABSTRACT

Natural products derived from plants have long been and will continue to be substantial sources of therapeutic agents in disease prevention and treatment. Resveratrol, which is a bioactive compound in a polyphenol structure, is found in significant amounts in several plant/food sources such as grapes, peanuts, strawberries, blueberries, pistachios, red mulberries, cranberries, and tomatoes. These functional foods rich in resveratrol be used widely owing to resveratrol does not show significant toxicity at low doses. Today, there is an increasing interest in polyphenols due to their antioxidant properties. The antioxidant effect of resveratrol underlies many of its medicinal effects, such as its neuroprotective and positive effect on neurodegeneration. In addition, it is outstanding with anti-inflammatory, antitumor, antiviral, antidiabetic, cardioprotective, and life-prolonging effects. Studies on resveratrol have previously focused on its pharmacological activities but recently have focused on its low bioavailability which poses a major problem to show the predicted effect.

INTRODUCTION

Resveratrol (*trans*-3,5,4'-trihydroxy-stilbene) is one of the outstanding phytochemicals in plant-based

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drug discovery and was first isolated from the roots of *Veratrum grandiflorum* by Takaoka in 1940, and *Polygonum cuspidatum* roots were later used for this purpose (Takaoka, 1940). Resveratrol contains two aromatic rings and three hydroxyl groups connected by an ethylene bridge.

The biosynthesis of resveratrol takes place through a combination of phenylpropanoid and polyketide pathways (Giovinazzo *et al.,* 2012). Resveratrol is widely in the families of Cyperaceae, Dipterocarpaceae, Fabaceae, Fagaceae, Liliaceae, Moraceae, Myrtaceae, Pinaceae, and Vitaceae, including species such as *Vitis vinifera*, *Arachis hypogaea*, *Morus rubra*, *Pistacia vera*, *Vaccinium myrtillus*, *Fragaria* L., and *Polygonum cuspidatum* (also known as Japanese knotweed/Itadori tea) (Tian & Liu, 2020). Vine and *P. cuspidatum* compared to other plant species; Its gained importance due to their high resveratrol capacity and widespread consumption of fresh or processed products (wine, vinegar, dried grape, e.g.) (Keskin *et al.,* 2009).

Glycoside forms of both *cis*- and *trans*- isomers of resveratrol exist in nature. The glycoside known as the major form of resveratrol is a resveratrol-3-*O*-β-D glycoside, also called "piseid or polydatin". In addition, there are different stilbene compounds in the dimer, trimer, and tetramer structure of resveratrol in nature. For example, the major oligomer ε-viniferin in grapes is the dehydrodimer of resveratrol. Various resveratrol oligomers have been identified in grapevine, including dimers, trimers, and tetramers derived from ε-viniferin (Niesen *et al.,* 2013; Romero-Pérez *et al.,* 1999; Udenigwe *et al.,* 2008). Resveratrol-derived dimers synthesized by oxidative coupling are in the structure of resorcinol. In addition to their antioxidant effects, they show neuroprotective, anti-HIV, and cytotoxic effects on various cell lines (Menezes & Diederich, 2019; Wang *et al.,* 2014).

Various extraction, separation/purification protocols, and chromatographic methods have been improved to optimize the extraction and isolation of resveratrol by researchers. Supercritical liquid extraction, High-speed counter-current chromatography, Ultrasonically Assisted Microwave Extraction (UAE), and High-performance liquid chromatography (HPLC)-Diode-Array Detection (PDA)-Electrospray Ionization (ESI) have come to the fore among separation-purification and identification methods. In these methods, optimum conditions are developed for parameters such as solvent type, temperature, and extraction time (Beyer & Biziuk, 2008).

Resveratrol is an important phytomolecule with its antioxidative, anti-inflammatory, antitumor, antiviral, antidiabetic, cardioprotective, protective against eye diseases, phytoestrogen, and life-extending properties (Colica *et al.,* 2018; Gündoğdu *et al.,* 2021). The French paradox has demonstrated that it has a preventive impact, especially in the case of coronary heart disease (Liu *et al.,* 2007).

Pharmacokinetic studies have become highly necessary to maintain its biological activity, keep it stable, and make it more resistant to oxidative degradation as resveratrol's structure is unstable when exposed to light. In light of these therapeutic effects and bioavailability of resveratrol, which can be used as a food/nutraceutical or medicine, well-formulated resveratrol-bearing tablets, capsules, nanoparticles, and controlled-release formulations based on encapsulating techniques such as solid lipid nanoparticles formulations should be used (Nunes *et al.,* 2020).

This chapter gives knowledge about resveratrol, advanced studies on its extraction, isolation, identification and bioavailability.

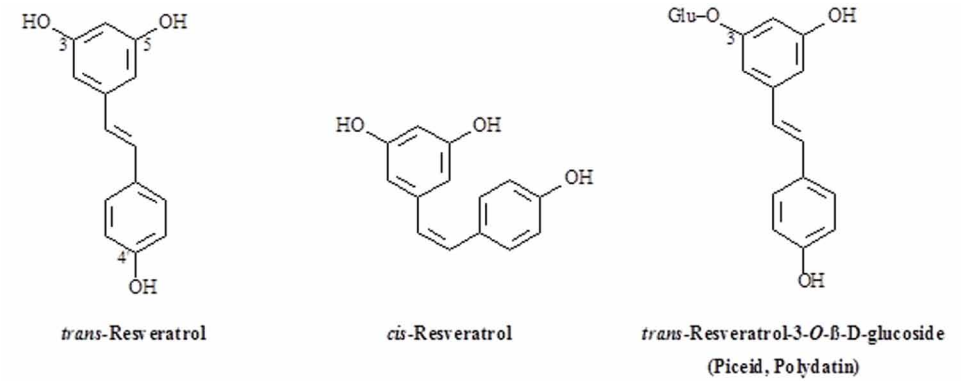
BACKGROUND AND MAIN FOCUS OF THE CHAPTER

Although the highest resveratrol content was is in *P. cuspidatum*, many other food sources such as grape (*Vitis vinifera*, *Vitis thunbergii*), peanut (*Arachis hypogaea*), strawberry (*Fragaria* L.), cranberry (*Vaccinium macrocarpon*), blueberry (*Vaccinium myrtillus*), peanut (*Pistacia vera*), red mulberry (*Morus rubra*), tomato (*Solanum lycopersicum*), *Phoenix dactylifera* and dark chocolate are among the rich sources of resveratrol. Therefore, the *P. cuspidatum* plant, which takes a significant place in the synthesis of resveratrol, has led to the rise of products with commercial importance (Huang *et al.,* 2005; Gündoğdu *et al.,* 2021; Tian & Liu, 2020).

Chemical Structure of Resveratrol

Resveratrol exists in nature as *trans*- and *cis*-isomers, commonly in the *trans*-form. However, its glycosylated form (*trans*-resveratrol-3-*O*-β-D glycoside, polydatin, piceid) is more stable and durable in oxidative degradation (Figure 30.1) (Şöhretoğlu *et. al.,* 2018; Venugopal & Liu, 2012).

Figure 1. Molecular structures of trans-resveratrol and piceid (Baur&Sinclair, 2006).



Trans-resveratrol is well-known to be abundant, particularly in the skins of colored grape types (0.30-14.10 mg/g fresh; 9.30-78.50 mg/g dry weight) (Keskin *et al.,* 2009). Although the high biological activities of *P. cuspidatum* are attributed to *trans*-resveratrol, as in grapes, the level of *trans*-resveratrol in *P. cuspidatum* is many times lower than the level of polydatin. For this reason, if hydrolyzed polydatin to resveratrol, the manufacture of resveratrol will be highly increased. At this point; extraction, isolation-purification, and identification techniques come to the forefront (Wang *et al.,* 2013).

Extraction and Isolation of Resveratrol

Among the many techniques for extraction of resveratrol, the most frequently used are Solvent Extraction (by shaking or Soxhlet apparatus), Microwave-Assisted Solvent Extraction, Ultrasonication Extraction, Microwave-Accelerated Extraction, Supercritical Fluid Extraction, and Membrane Extraction techniques. In these techniques, optimum conditions are developed for parameters such as solvent type, temperature,

Table 1. Some extraction and isolation-purification methods for resveratrol

Plant Sources	Extract	Extraction, Isolation-Purification Methods and Conditions	References
Polygonum cuspidatum Polygonaceae (Japanese knotweed)	95% Ethanol (EtOH)	Solvent Extraction, Liquid–Liquid Extraction (65 °C, 12h), Hydrolysis (pH=1, 75 °C, 8h) and HPLC (Nucleosil 100 C_{18} reverse-phase column)	Wang *et al.,* (2013)
	Methanol (MeOH)	Ultrasonication Extraction (45°C, 20 min) and Molecularly Imprinted Polymer-HPLC (Inertsil ODS-2 C_{18})	Zhuang *et al*., (2008)
	MeOH	Soxhlet Extraction (4 h), Supercritical Fluid Extraction (40 MPa, 100 °C, 45 min) and HPLC (C_{18} reverse-phase column)	Beňová *et al.,* (2010)
	Water (H_2O)	Supercritical CO_2 Extraction (30 MPa, 50 °C, 20 kg/h vCO_2)	Yu *et al.,* (2005)
	H_2O	Solvent Extraction and Enzymic Hydrolysis (pH=5, 50 °C, 24h)	Zhi-fang *et al.*, (2009)
	95% MeOH	High-Speed Counter-Current Chromatography (Spherigel ODS C_{18} column, 20 °C, 700 rpm)	Chu *et al.,* (2005)
	MeOH	High-Speed Counter-Current Chromatography (Shim-pack VP ODS column, 40 °C, 1500 rpm)	Yang *et al.,* 2001
Vitis vinifera Vitaceae	MeOH	HPLC (Hypersil Gold C_{18}, Nucleosil C_{18}, ODS Hypersil, Lichrospher 100-RP, Superspher RP-18)	Soleas *et al.,* 1997; Tzanova & Peeva, 2018
Vitis thunbergii Vitaceae	EtOH	Silica gel Column Chromatography [*n*-hexane−EtOAc (10:1, 5:1) and CH_2Cl_2−MeOH (15:1, 10:1, 5:1, 0:1)], Sephadex LH-20 [MeOH−H_2O, (3:1)], PTLC [(CH_2C_{12}−MeOH, 5:1)]	Huang *et al.,* 2005
Morus rubra Moraceae	EtOH: H_2O (80:20 v/v)	Solvent, and Solid Phase Extraction (60 °C, 30 min), HPLC (Discovery C_{18} column)	Shrikanta *et al.,* 2015
Arachis hypogaea Fabaceae	EtOH: H_2O (80:20 v/v)	Magnetic Solid Phase Extraction, LC-MS/MS (Hypersil Gold C_{18} column), HPLC-DAD (Nucleosil 120 C_{18}, $A_{l2}O_3$−ODS C_{18} column) and GC-MS (DB-5MS capillary column)	Ibern Gómez *et al.,* 2000; Lang *et. al.,* 2019; Tokuşoğlu *et al.,* 2005
Pistacia vera Anacardiaceae	EtOH: H_2O (80:20 v/v)	HPLC-DAD (Hypersil-ODS column) and GC-MS (DB-5MS capillary column)	Tokuşoğlu *et al.,* 2005

and extraction time (Beyer & Biziuk, 2008). Various protocols and combined chromatographic methods have been developed by researchers to optimize the extraction and purification of resveratrol from *P. cuspidatum* (Table 1).

For extraction, conventional methods (including distillation, liquid-liquid extraction, or Soxhlet extraction) by heating under reflux with methanol/ethanol are used. And then filtration, concentration, several clean-up steps, separation and purification (various column chromatographies) pursue. These methods, which are many inherent disadvantages, are usually time-consuming and require the disposal of plenty of toxic and unecological solvents (Beyer & Biziuk, 2008). For example, in a study comparing soxhlet and supercritical fluid extraction methods for the isolation of resveratrol from *P. cuspidatum* roots; although the time of the supercritical fluid extraction method is five times shorter than the extraction time of soxhlet, it has been reported that this technique is not very convenient for polar compounds such as resveratrol (Beňová *et al.*, 2010). In addition to new extraction methods such as microwave-accelerated extraction and supercritical fluid extraction, enzymatic hydrolysis is also preferred in obtaining high

recovery resveratrol from sources rich in polydatin (Zhi-fang *et al.,* 2009; Wang *et al.,* 2013). Also, the results of different studies displayed that the optimized High-Speed Counter-Current Chromatography method which eco-friendly extraction technology, can be used successfully for large-scale separation of resveratrol (Chu *et al.,* 2005; Yang *et al.,* 2001). Afterward this extraction, and isolation-purification study, resveratrol has been identified with various methods such as ^{1}H-^{13}C NMR, ESI-MS/MS (Chu *et al.,* 2005; Yang *et al.,* 2001; Wang *et al.,* 2013).

Pharmacokinetics and Bioavailability Enhancement of Resveratrol

Researchers investigated the pharmacokinetic parameters of resveratrol such as absorption, distribution, metabolism, and elimination in terms of many variables (dose, dosage form, administration, e.g.). *In vitro* and *in vivo* pharmacokinetic studies on resveratrol have revealed that, in addition to the administered dose-effect resveratrol absorption, the dosage form, route of administration, and diet have a substantial impact on resveratrol absorption (Huang *et al.,* 2019).

Resveratrol is rapidly absorbed by the gastrointestinal tract immediately after intragastric administration and reaches its maximum plasma concentration (C_{max}) within 30 minutes of high-dose administration (Soleas *et al.,* 2001). In an *ex vivo* percutaneous absorption assay, the plasma resveratrol level was 12.53 mg after 24 hours of administration of a cream containing a sustained release emulsion containing 20 mg of resveratrol. In addition, studies are reporting that the glycosylated form of resveratrol, which is steady and more resistant to oxidative degradation, is better absorbed from the human gastrointestinal system (Polonini *et al.,* 2014; Venugopal & Liu, 2012). The distribution of resveratrol, which has shown *in vivo* investigations to be localized in the liver, brain, gut, and adipose tissues, has not been fully characterized (Andres-Lacueva *et al.,* 2012). Afterward, resveratrol is exposed to a first-pass effect in enterocytes and hepatocytes following oral administration and is known to undergo subsequent glucuronidation (Lastra & Villegas, 2005). As with many bioactive ingredients, Phase II metabolic enzymes play a role in resveratrol biotransformation, and the effect of intestinal microbiota on metabolism is critical. So much the more, the UDP-glucuronosyltransferase (UGT) family appears to be prominent in the metabolism of resveratrol. The main glucuronides and sulfates of resveratrol are have been reported to resveratrol-3-*O*-glucuronide, resveratrol-*O*-glucuronide and resveratrol-3-*O*-sulfate, resveratrol-*O*-sulphate and resveratrol-3-*O*-disulfate, respectively (Wang & Sang, 2018). In the final step, resveratrol and its metabolites are eliminated in the urine. At this point, researchers have developed resveratrol-loaded microparticle and nanocapsule forms to delay the elimination, and it has been noted that it is eliminated more slowly compared to the standard form (Huang *et al.,* 2019). *In vivo* toxicity studies on rats, mice and rabbits showed that resveratrol at a dose of 0.75-210 g/kg/day was well tolerated and did not show any toxic effects (Crowell *et al.,* 2004; Williams *et al.,* 2009).

Due to the low bioavailability issues, studies on resveratrol have focused on enhancing bioavailability, and different dosage forms containing resveratrol have been tried considering pharmacokinetic and toxicity studies. In one of the bioavailability enhancing studies, it was observed that the antidiabetic effect of resveratrol on the pancreatic β TC cell line was increased (insulin secretion increased up to 85%) by loading resveratrol from new lipid-based, non-vesicular drug delivery systems into nanocochleates (Yücel *et al*., 2018). In a bioavailability enhancement study in C57BL mice has been reported resveratrol (100 mg/kg; oral gavage) or resveratrol (100 mg/kg; oral gavage)+piperine (10 mg/kg; oral gavage) was administered and serum resveratrol concentrations were measured in mice at periodic intervals. With the addition of piperine, the AUC and the maximum serum resveratrol concentration (Cmax)

increased to 229% and 1544%, respectively, thereby significantly improving the *in vivo* bioavailability of resveratrol (Johnson *et al*., 2011). On the other hand, zein nanoparticles which are inexpensive, safe, and effective choices for producing nanoparticles (NPs), have been prepared to improve the stability and oral bioavailability of resveratrol and loaded into zein NPs using the resveratrol nanoprecipitation method in recent times. As a result of this study, it was reported that zein NPs protect resveratrol from metabolization and resveratrol-loaded zein nanoparticles maintain their stability at +4 °C for at least one month (Nunes *et al*., 2020).

CONCLUSION

Resveratrol (3,5,4′-trihydroxystilbene) which is a well-known phytoalexin, has commonly been used in medicine, health products, and cosmetic industries on account of its various pharmaceutical and health-promoting properties such as anti-inflammatory, anticancer, cardioprotective, and life-extending effects. *Trans*-resveratrol is easy oxidizable and photosensitive, also poor bioavailability of resveratrol attributable to insufficient solubility, quick metabolism, and elimination led to limited practical applications of resveratrol in clinical. To benefit from the pharmacological effects of resveratrol, which can be taken as food/nutraceutical or medicine, the count of studies should be increased in which rapid, advanced, reproducible, and environmentally friendly advanced techniques are used instead of conventional methods for extraction, separation-purification, and identification. Then resveratrol-loaded tablets, capsules, and nanoparticle formulations with improved bioavailability should be developed.

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Chapter 18
Phytochemicals From Mangroves and Their Anti-Viral Applications

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ABSTRACT

Phytochemicals are recently gaining major attention for their therapeutic uses against several pathogenic viruses. Hence, searching for novel anti-viral molecules from plant sources is desirable as it is having fewer side effects. The mangrove plants are considered as an excellent source of phytomedicine due to production of several classes of phytochemicals. However, fewer studies have been conducted regarding the extraction of the potential anti-viral compounds from mangrove sources. In this chapter, an overview of isolation, extraction, and qualitative estimation of phytochemicals from the mangrove plants have been described. The major representative mangrove plant and its extracts that have shown potential anti-viral activity have been documented. Moreover, this chapter highlights the research-based analysis of potential anti-viral compounds from the plants in the mangrove ecosystem.

INTRODUCTION

Plant-derived compounds are being used as an important natural source of drug molecules and have gained importance in the medicinal chemistry. The parent molecules of most of the currently used medications have been derived from the plant. Also, due to their less toxic, and minimum side effects properties, the phytochemical is being preferred in therapeutic applications in comparison to synthetic drug molecules (Heywood, 2002; Sofowora *et al.,* 2013; Inoue *et al.,* 2019; Ghildiyal *et al.,* 2020). So, the researchers are currently emphasizing deriving new knowledge based on natural plant-based

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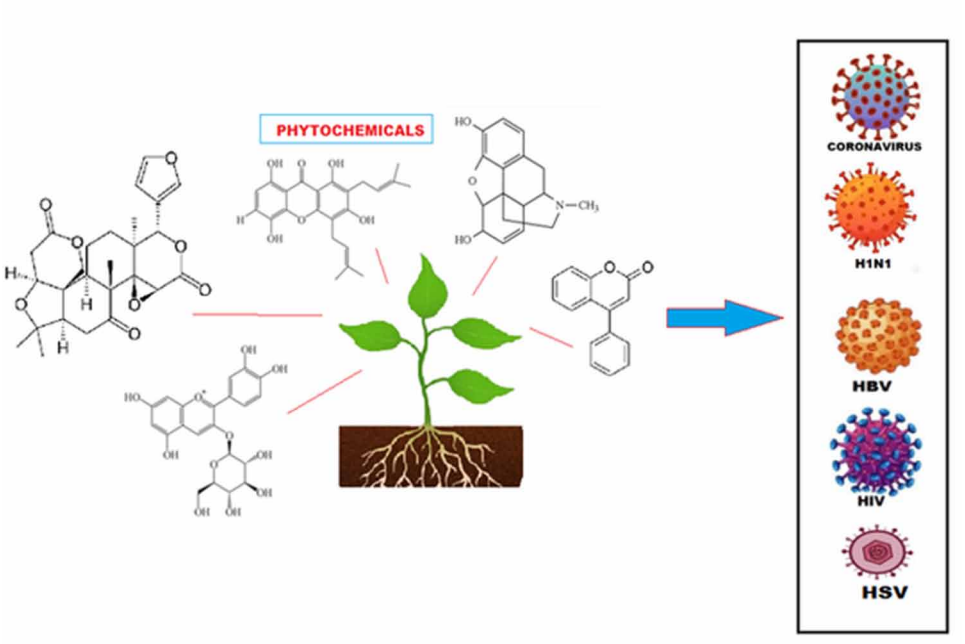
compounds for their potential use in the healing process of infectious diseases. The plants also contain several types of secondary metabolites with diversity in their molecular structure and functional properties. Many of the plant's secondary metabolites are effective in treating several metabolic diseases as well as infectious diseases. An experimental basis of the study of these secondary metabolites of the plants and their efficacy on the human disease treatment process has been performed. Several scientific studies have revealed the promising use of phytochemicals for the treatment of viral infections (Inoue & Craker, 2014; Satpathy, 2020; Kaur & Ahmed, 2021; Satpathy, 2021). The development of antiviral drug molecules is an important task to combat the life-threatening disease caused by the deadliest virus (Figure 31.1). Also, many of the viruses do not have established anti-viral treatment methods. Hence, due to the urgency is concern, suitable phytochemicals are to be explored scientifically as effective and inexpensive anti-viral inhibitor molecules (Ghorbanpour *et al.,* 2017). To date, several viral diseases have been reported and the mutant form of the deadly viruses are also occurring frequently. Among the emerging viral diseases, most of them are caused by pathogenic viruses like Human Immunodeficiency Virus (HIV), Influenza, Herpes simplex virus (HSV), Dengue, Chikungunya, Zika, Hepatitis B (HSB), Hepatitis C (HCV), Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and so on. Viral infections are associated with great health risks to human health. Also, the infection is difficult to control as the origin of new mutant forms of the viral strains. In the past, deadly viruses caused pandemics in the world thereby increasing the risk of spreading viral diseases between continents.

Very few drugs have been developed to date to effectively treat viral diseases. The majority of the approved antiviral drugs possess adverse drug reactions and have also developed viral resistance in long-term therapy. The infectious virus is a major cause of mortality in the recent few years. For instance, the infection by SARS–CoV-2 and influenza virus are responsible for over a million deaths throughout the globe (Gasparini *et al.,* 2012; Nováková *et al.,* 2018; Ben-Shabat *et al.,* 2020; Hafeez *et al.,* 2020). However, the repurposing method for the already reported phytochemical as an inhibitor for virus target is possible to study the antiviral property of the molecule. Although most of the antiviral drugs approved for the management of the viral disease are effective some of them have adverse reactions leading to raise the need for the development of plant-based drug development (Bahadur *et al.,* 2020; Anand *et al.,* 2021). Recently, the creation of SARS-CoV-2 virus-based pandemic situations and enhanced mortality rate in human beings have raised a serious global concern. Moreover, antiviral drugs also exhibit adverse side effects, which directly and indirectly affect human health. This provides opportunities for the development of plant-based drugs and herbal treatments with minimal side effects (Kapoor *et al.,* 2017; Irwin *et al.,* 2016; Biswas *et al.,* 2020).

Several targets in the viruses are available to which the specific phytochemicals are targeted and block the metabolism of the virus (Kumar & Pandey, 2013; Ahmad *et al.,* 2015; Lipson *et al.,* 2017; Subudhi *et al.,* 2018).

1. Receptor –host cell interaction that interferes with the host cell receptors
2. Binding to the replication enzymes to stop the replications
3. Binding to the other non-structural proteins to inhibit the key metabolic pathway such as replication and translation of the pathogenic viruses

Figure 1. Phytochemicals show activity against the target pathogenic virus



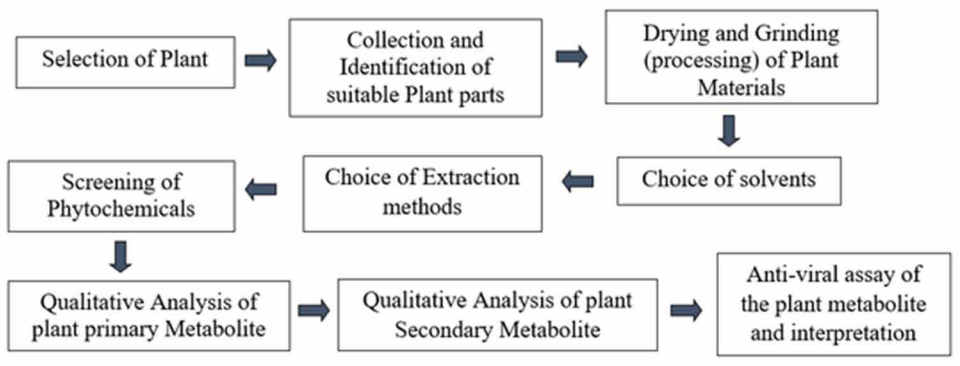
PLANT COMPOUNDS AS ANTIVIRAL AGENTS

As a treatment strategy, several categories of phytochemicals have been experimentally proved by researchers for showing their antiviral properties. For example, the activity of virus replication inhibitors has been described by researchers that show potential inhibitory effects against several viruses like Herpes Simplex Virus type 2 (HSV-2), HIV, Hepatitis B Virus (HBV), SARS–CoV. The crude extracts from the plants like *Andrographis paniculata* (Burm. f.) Wall. ex Nees., *Lindera chunii* Merr., *Dioscorea bulbifera* L., *Wisteria floribunda*. (Willd.) DC. have been shown to feature the antiviral feature (Mukhtar *et al.,* 2008; Bachar *et al.,* 2021; Adhikari *et al.,* 2021). The knowledge about the known bioactive compounds from plant sources can be repurposed against other pathogenic viruses, the same has been successfully evaluated by many researchers (Choi *et al.,* 2019; Calabrese *et al.,* 2000; Mpiana *et al.,* 2020; El-Ansari *et al.,* 2020; Amparo *et al.,* 2021).

METHOD OF ISOLATION OF PHYTOCHEMICALS FOR THERAPEUTIC USE

To enhance the scientific value, before isolation of bioactive constituents from the plants, it is essential to identify the plant and the plant parts that produce the specific phytochemicals. The selection can be based on the traditional knowledge about the use of the plant as anti-viral therapy. Also, sometimes the ecological factor is taken into consideration since the plant can produce more specific categories of secondary metabolites that can be used as antiviral agents. Additionally, the plant selection can be performed based on the published literature, toxic compounds that produce and therapeutic importance of the plant and so on. The collected and identified plant material is initially kept for drying below 300 ^{0}C

Figure 2. Standard procedure followed for identification of antiviral metabolites from the plants.



also it should be protected from exposure to direct sunlight to avoid the chemical change of the molecule by electromagnetic radiation. Alternatively, the plant material can also be milled using the help of an electric grinder or by mortar and pestle (Velavan, 2015).

The standard procedure that is followed in the screening of phytochemical extraction to antiviral assay has been shown in Figure 2. The rate of success for the isolation of active phytochemicals is also mostly dependent on the type of solvent used in the extraction process. Several chemical properties such as low toxicity, evaporation at low heat, and high preservative potential of solvent are preferred during the extraction process. In general, various solvent systems like acetone, alcohol, chloroform, ether, and Dichloromethanol are used including water. Some of the popular extraction methods are being used in the phytochemical extraction process are described in Table 1.

SCREENING METHODS OF PHYTOCHEMICALS

The bio-active phytochemicals are generally occurred in the plants in the form of different metabolites. Hence, a preliminary qualitative mode of phytochemical analysis of the medicinal plants' metabolites is essential to confirm the presence of types of phytochemicals present in the extract (Starmans & Nijhuis, 1996; Savithramma & Suhrulatha, 2011). The methods adopted for qualitative analysis of major phytochemicals have been described in Table 2.

APPLICATION AND IMPORTANCE OF MANGROVE PLANTS AND PHYTOCHEMICALS IN ANTIVIRAL THERAPY

In consideration of the habit and habitat of different medicinal plant species, the mangroves exhibit special attention. These plants are perennial and usually grow in the tropical coastal wetlands area. These plants (mostly trees and shrubs) grow in shallow water where the water is generally brackish. Since the mangroves survive in harsh ecological conditions, they are highly adapted internally (anatomically, physiologically, and morphologically). Due to their rich biodiversity, mangrove forests are considered one of the hot spots of the wetland ecosystem (Kathiresan & Bingham, 2001).

Table 1. Major types of extraction methods of phytochemicals

Name of the method	Description	References
Soxhlet extraction	• In this process, the compound is isolated from the plant extract by a repetitive procedure by using a nearly equal volume of solvent in each cycle followed by solvent evaporation. • This dried and plant sample is kept in the Soxhlet apparatus that facilitates the extraction of the different phytochemicals based on the types of the solvent used in the extraction method. • After the end of each cycle of extraction, the solvent extract is evaporated by a rotary evaporator in a vacuum environment. • One of the major advantages of the use of the Soxhlet apparatus is less amount of solvent is required.	Mitra *et al.,* (2021)
Accelerated solvent extraction	• In this type of extraction method, the plant material is packed with a solid support such as sand. The application of the organic solvents with the high temperature and pressure accelerates the extraction process by the process of diffusion. • Since the method uses a small amount of solvents hence considered more efficient as compared to the Soxhlet extraction method.	Sharma & Kaushik, (2021)
Supercritical fluid extraction (SFE)	• This type of extraction method of phytochemicals involves the principle of critical points, a particular condition in which the liquid state and vapor state co-exists (properties of both states). • In this method, the supercritical fluid (SCF) is applied to the plant material at a high pressure contained in a cylinder and the extract is collected in a separate chamber. • This is mainly used to extract the non-polar and thermo-labile phytochemicals.	Arumugham *et al.,* (2021)
Microwave Assisted Extraction (MAE)	• Microwave assisted extraction (MAE) is the best suitable for thermolabile substances. • The principle reveals, that microwaves cause a dipole rotation effect in organic molecules and due to the subsequent heating process lead to the destruction of hydrogen bonding. • Destruction of hydrogen bonding also related to the enhanced penetrating property of the solvents into the plant matrix • The removal of moisture if any from the dried form of the plant material is removed by high temperature and pressure generated due to microwave radiation. • Once the extraction process is completed, the separation of compounds from the solvents is done by using the processes like distillation.	Sharma *et al.,* (2020)
Maceration	• One cost-effective method is used for the extraction of bioactive phytochemicals. • The plant material is initially grounded into smaller particles to enhance the surface area before the addition of the solvents • The powdered plant material is then soaked in desired solvents for kept for hours/ days to facilitate the diffusion process. • The extract is prepared by filtration followed by the concentration in a rotary evaporator by evaporating the solvent.	Abubakar & Haque, (2020)

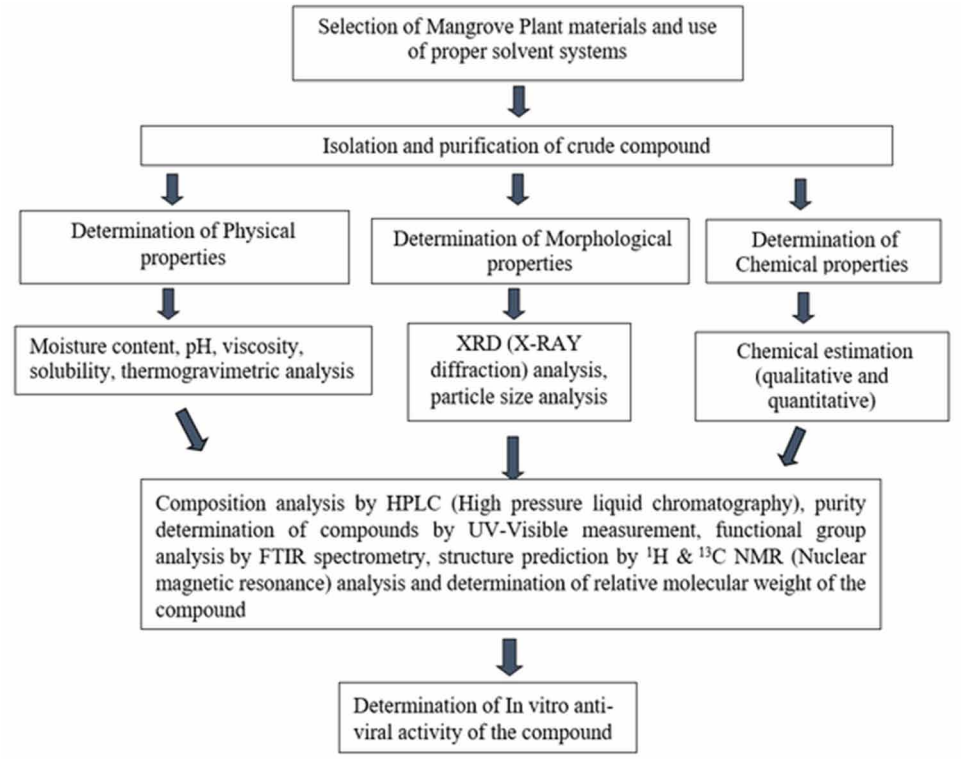
Research has been confirmed about the mangrove plants as an important source for the search for novel drug molecules due to their ecological adaptation leads to the synthesis of large numbers of phytochemicals. Among these phytochemicals, many show significant pharmacological properties and are used as active antiviral, antibacterial and antifungal compounds (Bandaranayake, 1998; Abeysinghe, 2010; Aljahdali *et al.,* 2021). The biochemical investigations on several mangrove species have shown that the plants are a rich source of a variety of bio-active compounds such as alkaloids, flavonoids,

Table 2. Qualitative assay methods of major phytochemicals

S.No.	Phytochemical types	Assay methods (reagents used)	Observations (Test of conformation)
1	Terpenoids	Addition of the acetic anhydride to the plant extract followed by concentrated $H_2 SO_4$ addition	Formation of blue, green rings
2	Tannins	Addition drops of 1% lead acetate to the plant extract	Yellowish precipitate
3	Saponins	The plant extract is mixed with distilled water followed by agitation in a graduated cylinder for 15 minutes.	Formation of foam
4	Anthocyanins	Aqueous plant extract is to be added with 2N Hydrochloric acid (HCL) and ammonia.	Appearance of pink-red turns blue-violet
5	Coumarins	Plant aqueous extract is to be added with 10% NaOH	The formation of yellow color indicates
6	Emodins	NH_4OH and Benzene are to be added to the phyto extract.	Appearance of red color
7	Steriods	Plant extract in the chloroform solvents is to be added with an equal volume of concentrated sulphuric acid	The upper layer turns red and Sulphuric acid layer shows yellowish green fluorescence.

triterpenoids, polyphenolic compounds, xanthones, coumarins, tannins, and so on (Vadlapudi & Naidu 2009; Abeysinghe *et al.,* 2006). Hence, these bioactive compounds of mangrove plants are frequently used as drugs against various critical human diseases (Kokpol *et al.,* 1990; Reddy & Grace 2016; Ad-

Figure 3. Showing experimental determination of bioactive compounds from the mangrove plants



hikari *et al.,* 2017). Many species of mangroves are frequently used in the traditional medicine systems to treat several human health disorders. The therapeutic properties of the mangrove plant product are based on its phytochemical composition and the mangroves are known to possess different categories of secondary metabolites used to treat several human diseases (Premanathan *et al.,* 1994; Mitter & Jadhav 2011; Piyusha *et al.,* 2012). The common steps that are adapted for the extraction and characterization of potential phytochemicals from the mangroves have been shown in Figure 31.3. Specifically, several antimicrobial metabolites extracted from the mangrove plants have shown their antibiotic reactions on many pathogenic microbial genera like *Shigella*, *Staphylococcus*, *Escherichia,* and *Penicillium* (Kokpal *et al.,* 1990).

Usually, the bioactive compounds of the mangrove plants are obtained in the form of primary or secondary metabolites. The knowledge of the chemical constituents of these plants is desirable to understand the composition of the herbal drugs and their formulation (Premanathan *et al.,* 1996; Poompozhil & Kumarasamy, 2014). Several workers have evaluated the effectiveness of mangrove plants in traditional medicine. For example, the qualitative and quantitative analysis of *Laguncularia racemosa* (L.) Gaertn. f. leaves has indicated the presence of many phytochemicals (secondary metabolites) and can be tested for their effectiveness against several diseases (Quraishi *et al.,* 2015) . Meenakshi and Jayaprakash formulated a new type of pesticide from the mangrove plant *Rhizophora mucronata* Lam. that can be used as a natural eco-friendly effective mosquito repellent to control vector-borne diseases (Meenakshi & Jayaprakash, 2014). Similarly, Joel and Bhimba experimentally studied the antioxidant and thrombolytic properties of the *Rhizophora mucronata* Lam. phytochemicals (Joel & Bhimba 2010). Eswaraiah et al. (2020), studied the anti-microbial action of the leaf extract bioactive compounds of several mangrove plants and proved their activity against pathogenic strains (Eswaraiah *et al.,* 2020). Some more examples have been documented in the table given below (Table 3).

CHALLENGES AND OPPORTUNITIES IN DISCOVERING THE MANGROVE PHYTOCHEMICALS FOR THE ANTIVIRAL THERAPY

The global research strategies for the discovery of antiviral compounds from mangrove plant sources are showing an increasing trend (Figure 4). The selection, identification and extraction procedure of anti-viral phytochemicals from the mangrove plants are directly linked to the therapeutic applications. The discovery of novel methods for the low-cost and safe extraction methods of bioactive compounds from mangrove plants is a challenging task. Also, during the extraction process care should be taken for the interference of other phyto-based contaminants with the target compound (Kwon *et al.,* 2017; Stéphane *et al.,* 2021).

After successful isolation and extraction, another most challenging task is to successfully prove the antiviral property of the compound and the formulation of the correct dose. Phytochemicals having antiviral activity can be nano-encapsulated for better delivery, prolonged action, and enhanced bioavailability. Moreover, excessive research on different biodiversity-rich regions could be explored to get more potent phytochemicals and metabolites as antiviral agents. Due to the presence of diverse phytochemicals in the mangroves, it is expected that the mangroves contain the effective bioactive compound that may use against several pathogenic viruses. Hence, the multiple virus target hitting nature of these compounds is to be explored. In this aspect, the computational analysis might play a major role in the prediction method due to its robustness and low-cost nature. Several computational analyses such as molecular

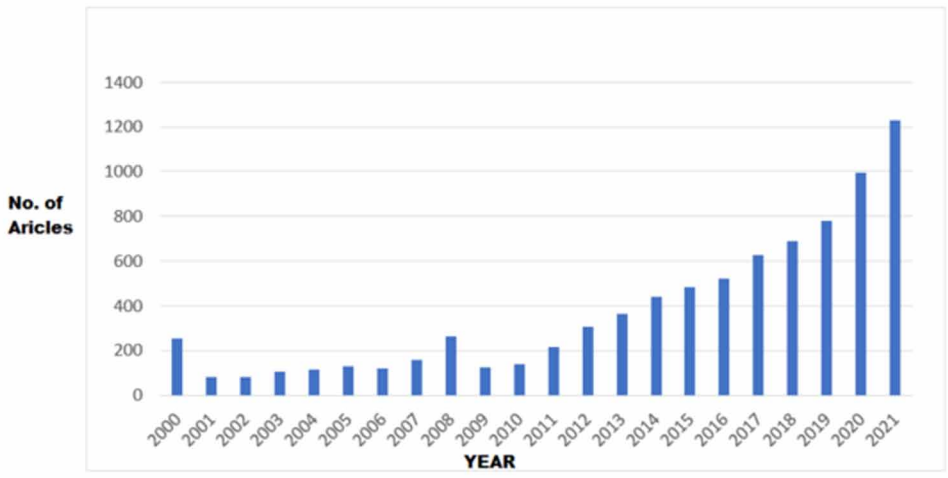
Table 3. Some of the representative mangrove plants produce phytochemicals are being used for Anti-viral therapy.

Name of the plant	Family	Bioactive compounds	Target virus	References
Avicennia officinalis L.	Acanthaceae	Crude Plant extract	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2)	Mahmud *et al.,* (2021)
Aegiceras corniculatum (L.) Blanco	Primulaceae	Cyclopentenone	Influenza A virus (H1N1)	Zhang *et al.,* (2011)
Acanthus ilicifolius (L.)	Acanthaceae	2-benzoxazoline	hepatitis B virus (HBV)	Nabeelah Bibi *et al.,* (2029)
Avicennia marina (Forssk.) Vierh	Acanthaceae	Crude plant extract	Human Immunodeficiency Virus, Herpes Simplex Virus (HSV)	Namazi *et al.,* (2013)
Bruguiera cylindrica (L.) Blume	Rhizophoracea	Extract from bark, fruit, leaf, hypocotyl	Hepatitis B virus (HBV)	Premnathan *et al.,* (1992)
Ceriops decandra (Griff.) Ding Hou	Rhizophoraceae	Phenolics and Flavonoids	Hepatitis B virus (HBV)	Krishnamoorthy *et al.,* (2011)
Clerodendrum inerme (L.) Gaertn	Lamiaceae	Phenolic, steroids, di- and triterpenes, flavonoids, volatile oils	Hepatitis B virus (HBV)	Chakraborthy & Verma (2013)
Callophylum inophyllum L.	Callophyllaceae	Benzopyrans, coumarins, steroids, triterpenes, xanthones	Human Immunodeficiency Virus (HIV)	Govindappa *et al.,* (2015)
Pistacia integerrima J. L. Stewart ex Brandis (PI)	Anacardiaceae	28-demethyl-beta-amyrone, 24-Noroleana-3,12-diene, and stigmasterol	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2)	Paul *et al.,* (2022)
Pandanus odorifer (Forssk.) Kuntze	Pandanales			
Pongamia pinnata (L.) Pierre	Fabaceae	Seed extract	Herpes Simplex Virus (HSV)	Elanchezhiyan *et al.,* (1993)
Rhizophora apiculata Blume	Rhizophoracea	Carbohydrate extract	Human Immunodeficiency Virus (HIV)	Premanathan *et al.,* (1999)
Rhizophora mucronata Lam.	Rhizophoracea	Polysaccharide extract	Human Immunodeficiency Virus (HIV)	Premanathan *et al.,* (1996)
Rhizophora lamarckii Montr	Rhizophoracea	Crude plant extract	Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV)	Premanathan *et al.,* (1996)
Sonneratia apetala Buch.-Ham	Lythraceae	Anthroquinoid, triterpenes and steroids, gibberellins, carboxylic acids and lactones, polyphenols,	Hepatitis B virus (HBV)	Bandaranayak, (2002)
Sesuvium portulacastrum L.	Aizoaceae	Crude Leaf extract	Hepatitis B virus (HBV)	
Salicornia brachiata Roxb.	Amaranthaceae	Crude Leaf, stem extract	Hepatitis B virus (HBV)	Dhawan, (2012)
Suaeda maritima (L.) Dumort.	Amaranthaceae	Steroid, triterpenes	Hepatitis B virus (HBV)	
Sonneratia paracaseolaris	Lythraceae	Triterpenoids	Influenza A virus (H1N1)	Gong *et al.,* (2017)
Xylocarpus granatum J. Koenig	Meliaceae	Limonoids	Human Immunodeficiency Virus (HIV)	Dai *et al.,* (2017)
Xylocarpus moluccensis (Lam) M.Roem.	Meliaceae	Limonoids	Influenza A virus (H1N1)	Li *et al.,* (2015)

docking and molecular dynamics simulation have been frequently used to establish phytochemicals as anti-viral compounds. Many of the phytochemicals from the mangrove sources have been identified to

have an effective anti-viral nature. Hence, these identified compounds can be used for the repurposing of the drug against other related pathogenic viruses (Murugan *et al.,* 2021; Mahmud *et al.,* 2021; Kharisma *et al.,* 2021).

Figure 4. Year-wise publication of research article when searched in Google scholar (https://scholar.google.com/) with the keyword antiviral compounds and Mangrove plant.



CONCLUSION

Traditionally the bioactive phytochemicals plants have been continuously exploited in the field of the healthcare system for antiviral therapy. Plant product-based therapy is a preferred mode of medication that is associated with less toxicity and minimal side effects. Several phytochemicals from the mangrove source have been screened and identified for the treatment of pathogenic viruses such as influenza, dengue, chikungunya, HIV, SARS-CoV-2 and so on. Mangrove plants have been used as a traditional medicine for a long day, however, specifically the anti-viral compounds from the mangrove plant are less exploited. In this chapter, a compressive review has been made to provide some of the important information about the mangrove plants and their phytochemical constituents used as anti-viral agents. Additionally, the common extraction and screening procedures that are frequently used for phytochemicals have been presented. Also, the challenges and opportunities associated with the discovery of bioactive compounds from mangrove plants have been discussed. Moreover, this chapter provides a thorough analysis and discussion of different types of mangrove plants and their specific phytochemicals that contain the metabolite having anti-viral properties by narrating the recent literature. It is expected that the scientific analysis and screening of novel mangrove phytochemicals can be suitably used for the development of potential antiviral drugs.

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Chapter 19
Anticancer Effect of *Aristolochia tagala* and *Curcuma caesia* Acting Through Tumor Necrosis Factor-α: Mediated Nuclear Factor κB Pathway

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ABSTRACT

This chapter begins with a brief description of the events associated with carcinogenesis such as what led a normal cell to transform into a pre-neoplastic one, their multiplication, and development into cancer. The authors also described how reactive oxygen species (ROS) are generated endogenously and from carcinogens, their role in carcinogenesis, and the link between inflammation and cancer. Elucidation of how cancer arises contributes to understanding the molecular mechanisms of action of some natural products. Herbal natural products contain metabolites that exert a physiological action on human body. These metabolites are used therapeutically in modern medical practices to prevent and cure various diseases including cancer. This chapter discusses the anticancer property of two herbal plants Aristolochia tagala Cham. and Curcuma caesia Roxb. in diethylnitrosamine-induced mouse liver cancer and describes the most probable molecular mechanisms of action of the metabolites present in these plants contributing to their anticancer effect.

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INTRODUCTION

Carcinogenesis is a term that describes the process that occurs during tumor cell transformation. Both genetic and epigenetic factors are involved in the disruption of normal cell growth and its control leading to the development of cancer. These factors play a role in each of the different stages of carcinogenesis which are initiation, promotion and progression. A change in the genetic makeup of cell can lead to alterations of four broad categories of cancer genes, namely the activation of oncogenes, inactivation of tumor suppressors, evasion of apoptosis genes, and defective DNA repair genes (Malarkey *et al*., 2013). Selective clonal expansion of mutated cells leads to the appearance of a benign lesion or preneoplastic focus and rapid growth of these cells enhances the probability of accumulation of additional genetic damage (Mehta, 1995; Gomes-Carneiro *et al*., 1997). Additional mutations and structural variation in chromosomes lead to a formation of neoplastic and metastasized cells which are invasive, fast growing and have biochemical, metabolically and morphological characteristics different from normal healthy cells (Pitot & Dragan, 1991; Butterworth*et al.,* 1998, Klaunig *et al*., 2000).

Endogenous and environmental factors are known to play a role in the progression of carcinogenesis which involves different biochemical mechanism and genetic elements. Endogenous factors include unavoidable spontaneous mutations that arise as a result of random errors in DNA replication, hormonal imbalance, growth factors and complex endogenous processes like ageing, inflammation, and obesity. These factors are together influenced by the exogenous or environmental factors and hereditary (Pitot, 1991; Wu *et al*., 2018). Many environmental factors have been shown to be carcinogenic. The environmental factors can be broadly divided into (a) **Physical factors** which comprises of ionizing radiations (IR) and UV light (b) **Chemical factors** like benzo[α] pyrene, heterocyclic amine, ethyl alcohol, aflatoxin, asbestos, cadmium, etc. and (c) **Biological factors** likehepatitis B virus, hepatitis C virus, epstein-Barr virus (EBV), human herpesvirus 8 (HHV-8), HTLV-1 (human T-lymphotrophic virus type 1), human papilloma virus (HPV).

ROS INVOLVEMENT IN CARCINOGENESIS

Reactive oxygen species collectively refers to radicals, ions or molecules that have a single unpaired electron in their outermost shell of electrons. ROS are unstable and highly reactive. Superoxide ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$), nitric oxide ($NO^{\bullet}$), organic radicals ($R^{\bullet}$), peroxyl radicals ($ROO^{\bullet}$), etc. are categorized as free oxygen radicals. Hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), ozone/trioxygen (O_3), organic hydroperoxides (ROOH), hypochloride (HOCl) etc. are categorized as non-radical ROS (Liou & Storz, 2010).

ROS are produced endogenously as byproducts of oxygen metabolism. During mitochondrial oxidative metabolism, single electron reduction of O_2 leads to the production of $O_2^{\bullet -}$ in the mitochondrial matrix. The mitochondrial electron transport chain is the major contributor of endogenous ROS in mammalian tissues (Saybaşili *et al*., 2001; St-Pierre *et al*., 2002; Klaunig & Kamendulis, 2004). Enzymatic reactions catalysed by NADPH oxidase, xanthine oxidase, lipoxygenases and cylooxgenases within the cells also contributes to the ROS pool (Babior, 1999; Griendling *et al*., 2000; Curtin *et al*., 2002; Schrader & Fahimi, 2006; Sharan *et al*., 2011). Superoxide can be converted to hydrogen peroxide (H_2O_2) (Juarez *et al*.,2008) and H_2O_2 generated can be converted to hydroxyl free radicals via the Fenton reaction (Winterbourn, 1995).

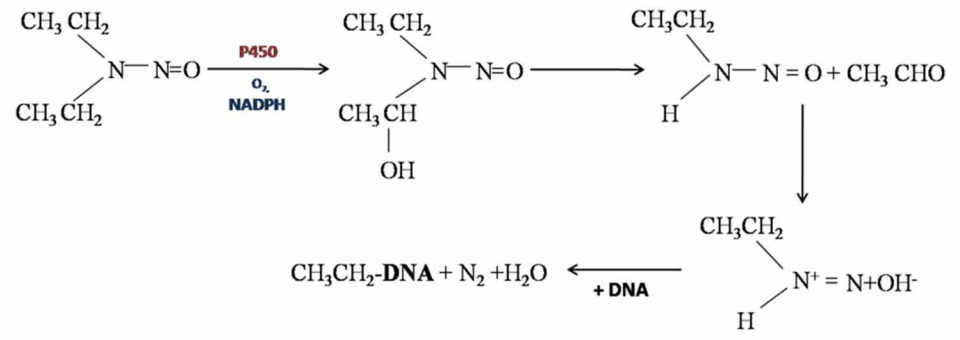
Exogenous sources of ROS include radiation, drugs and chemicals, heavy metals, pollutants, viruses etc. Exposure to ionizing radiation (IR) can directly disrupt atomic structures producing chemical and biological changes or it can lead to production of ROS such as e^-_{aq},$^{\bullet}OH$, $H^{\bullet}$, H_2, and H_2O_2 by radiolysis of water. IR also stimulates inducible nitric oxide synthase (NOS) activity in cells generating nitric oxide ($NO^{\bullet}$). Indirect effects of low linear energy transfer (LET) IR such as γ-rays and X-rays modulates the extent of production of these species. As water content in the cells is high these free radicals and electrons react with it and other oxygen molecules to produce superoxide anion radical ($O_2^{\bullet-}$) which is highly reactive and can further react with nitric oxide ($^{\bullet}NO$) to produce peroxynitrite anion ($ONOO^-$). The ROS generated ultimately in turn attack other critical molecules (Azzam *et al*., 2012).

Simultaneous induction of several ROS-producing pathways and enzymes by biological agents such as virus can cause oxidative stress. Respiratory viruses, hepatitis C virus (HCV), human papailioma virus (HPV) triggers enzymes like the nicotinamideadenine dinucleotide phosphate oxidases (NADPH oxidases, Nox) and xanthine oxidase (XO), cytochrome P450 2E1 (CYP2E1) and ER oxidoreductin 1α (Ero1α). Production of ROS is also induced by viral proteins. One mechanism of ROS production induced by HCV involves localization of its core proteins on mitochondrial membrane or by binding to heat shock protein 60 (Hsp60) in mitochondrial matrix. This causes accumulation of calcium ions in mitochondria which alters normal functioning of the respiratory chain (Marco *et al*., 2013; Ivanov *et al*., 2017; Khomich *et al*., 2018). Chronic HCV infection leads to steatosis and the accumulated free fatty acid enhance production of reactive oxygen species (ROS), causing mitochondrial dysfunction and endoplasmic reticulum stress (Irshad *et al*., 2017).

Both natural and synthetic compounds can be factors for cancer development. Certain chemicals or combination of chemicals can induce carcinogenesis upon exposure (Luch, 2005). The mode of absorption and distribution of these compounds to several tissues depends on their physicochemical properties (King *et al*., 1995; van Leeuwen & Zonneveld, 2001). Chemical carcinogens can be classified as genotoxic carcinogens i.e. they directly react with DNA through the formation of covalent bonds resulting in DNA-carcinogen complexes called as DNA adducts or nongenotoxic carcinogens i.e. they do not react directly with DNA. They can be cytotoxic or mitogenic in function. Mitogenic compounds induce cell proliferation in target tissue through interaction with a specific cellular receptor and cytotoxic carcinogens cause cell death in susceptible tissues (Cohen 1991; Cohen *et al*., 1992; Butterworth & Bogdanffy, 1999; Luch, 2005). The dead cells/necrotic cells are removed by cells of the immune system through a series of biochemical processes which leads to production of ROS (Lutz, 1998; Ohshima *et al*., 2005). Genotoxic carcinogens usually require metabolic activation of the parent compound to a highly reactive compound. The reactive compound interacts with cellular DNA or enzymes involved in DNA repair causing a mutation in the DNA (Miller, 1970). The metabolic activation usually takes place in the liver where cytochrome P450 is in abundance. Nitrosamines, carbon tetrachloride (CCl_4), aflatoxins, etc. are metabolically activated and act like free radicals, significantly increase superoxide radical ($O_2^{\bullet-}$) concentration in the liver and damage various biological systems (Recknagel *et al*., 1989; Nordmann *et al*., 1992).

Diethylnitrosamine (DEN), a thoroughly studied carcinogen is metabolically activated to produce α-hydroxyl nitrosamine in liver (Figure 32.1). The hydroxylation process is carried out by cytochrome P2E1; an isozyme of the P450 complex (Sharan and Wary, 1992; Verna *et al*., 1996; Wary and Sharan, 1999). The electrophilic ethyldiazonium ion reacts with DNA bases to form promutagenic adducts O^6-ethyl deoxy guanosine and O^4 and O^2- ethyl deoxy thymidine that can produce DNA chain damage, depurination or binding to DNA increasing the ROS pool. Exposure to DEN also caused an increase level of 8-OHdG and its generation was at an early stage of exposure which reflects the oxidative dam-

Figure 1. Biotransformation of DEN and mechanism of DNA-adduct formation. (Source: Verna 1996, Wary & Sharan 1991, Sharan & Wary 1992).

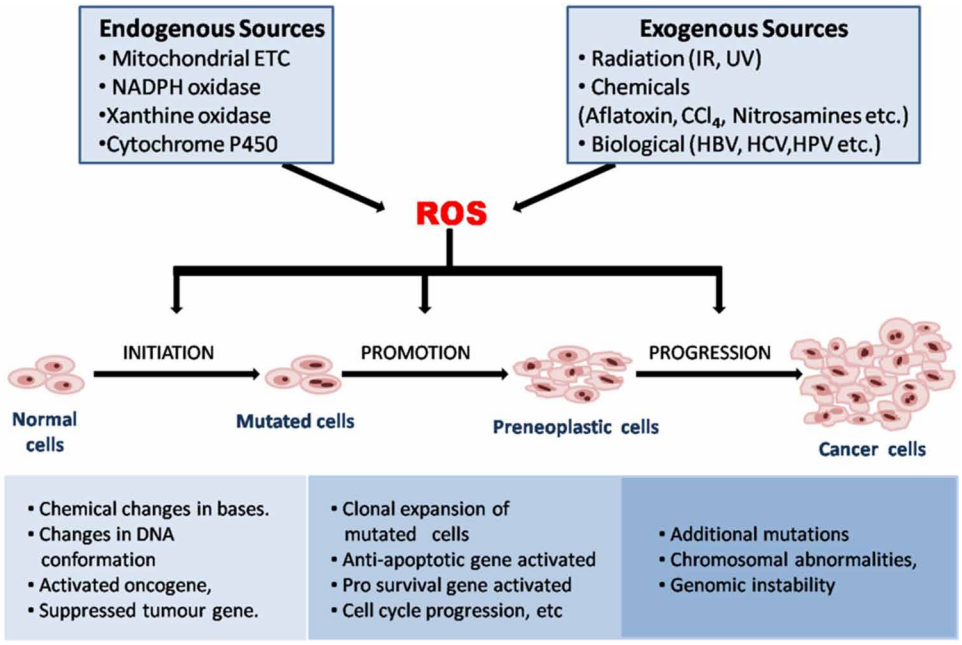


age to DNA (Nakae *et al*., 1997). 8-OHdG can pair with both cytosine and adenine causing a GC to TA transversion. Mutated oncogenes and tumour suppressor genes contain these nucleotides (Shibutani, *et al*., 1991; Cheng *et al*., 1992; Grollman & Moriya, 1993). During DNA replication, OH8dG is incorporated into the daughter strand complementing dC or dA on the template strand resulting in AT to CG transversions (Cheng *et al*., 1992; Demple & Harrison, 1994). DEN caused *Ha*-ras, *B-raf* and *Ctnnb1mutations* (Tolba *et al*., 2015). Metabolic activation of DEN leads to formation of lipid radicals in the whole body of exposed animals and also caused lipid peroxidation. The lipid radicals are generated through microsomal metabolism. This indicates that free radical intermediates play an important role in the initiation of hepatic carcinogenesis by DEN (Bartsch *et al*., 1989; Yamada *et al*., 2006).

ROS are important for cellular homeostasis. At low or regulated levels, ROS are involved in many vital physiological processes. They serve as signaling molecules and response to growth factor stimulation and control of inflammatory responses. They are responsible to regulate numerous physiological and cellular processes including cell differentiation, proliferation, apoptosis, and adaptation to hypoxia, cytoskeletal regulation, migration and contraction (Krause, 2007; Finkel, 2011; Holmstrom & Finkel, 2014; Schieber & Chandel, 2014). Under normal physiological conditions, ROS are steadily maintained to prevent cells from oxidative damages. The stable concentration of ROS in cells is maintained by detoxifying enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), Phase II enzymes (e.g., glutathione transferase, NAD(P)H: quinone reductase, UDP-glucuronosyltransferases) that specifically scavenge different kinds of ROS. The nonenzymatic component which includes scavenger molecule glutathione, beta-carotene, vitamin A, ascorbic acid (vitamin C) and alpha-tocopherol (vitamin E) are also involved in maintaining redox equilibrium (Mataix *et al*., 1998). Cellular levels of reactive oxygen species can increase due to overproduction and diminished elimination. This can be due to increased metabolic activity, mitochondrial dysfunction, oncogene activation which enhanced metabolism or loss of tumor suppressor which diminish ROS elimination (Trachootham *et al*., 2009). Exposure to environmental factors can also lead to increase in cellular ROS. The incidence of cancer is seen to be directly linked to exposures to environmental factors. Most environmental factors can directly or indirectly generate ROS which plays an important role in carcinogenesis. At the initiation stage of carcinogenesis, ROS is involved in changing the genetic makeup of cell which occurs through formation of oxidative DNA adducts leading to mutations (Dizdaroglu, 1992; Demple & Harrison, 1994; Lu *et al*., 2001; Odyuo &Sharan, 2005; Bhattarcharjee & Sharan, 2008). DNA stand breakage, nucleotide

modifications, deoxyribose modification and DNA cross-linking are results of ROS reaction with DNA. If the oxidative damages to DNA are not repaired before replication processes, then it will lead to further mutation in DNA, genome instability, more errors in replication and cell death (Marnett, 2000; Cooke, 2003; Klaunig & Kamendulis, 2004; Valko *et al*., 2006). Disruption or activation of genes responsible for regulation of cell growth, survival, and senescence allows mutated cells to proliferate leading to accumulation of preneoplstic cells within a tissue (Mehta, 1995; Gomes-Carneiro *et al*., 1997). Alteration in the expression of cytokine growth factors e.g. tumour necrosis factor-α, interleukins etc. increases cell proliferation. ROS can influence Ca^{2+}channels/pumps/exchangers and can lead to increase in concentration of Ca^{2+} ions within the intracellular area, this can results in activation of proto-oncogenes such as c-fos, c-jun, c-myc or activated protein kinase C (PKC), Notch1/Nrf2 and other signalling pathways involved in cell migration and invasion leading to cancer progression (Klaunig & Kamendulis, 2004; Wu, 2006; Strzelczyk & Wiczkowski, 2012; Zhang *et al*., 2016; Aggarwal *et al*., 2019).

Figure 2. Reactive oxygen Species (ROS): Sources, roles in cellular function and their implications on cancer (Matés &Sánchez-Jiménez, 1999 with modification)



INFLAMMATION AND CANCER

Inflammation is an immune response that is triggered when the host is exposed to certain external stimulus. Activation of inflammatory signals occurs to repair tissues damage and eliminate a damaging agent. Upon exposure to infections, radiations or chemicals, inflammatory cells, macrophages and mast cells that release cytokines like TNF-α, IL-1β, IL-6 and pro inflammatory chemokines like IL-8, MCP-1,MIP-1α stimulate attraction of circulating leukocytes to the site of inflammation to eliminate the pathogen, initiate healing and generate immunological memory. This type of inflammation is acute

inflammation and it is a physiological process and a host defensive response. Persistent inñammation due to continuous exposure to infections/insults leads to chronic inñammation causing further damage and increasing the risk of cancer. About 15-20% of all death from cancer worldwide is associated with chronic inflammation caused by infection or physicochemical agents (Prete *et al*., 2011; Korniluk *et al*., 2017; Zhang*et al*., 2017; Monkkonen & Debnath, 2018). Hepatocellular carcinoma (HCC) can arise due to chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV). Infection with *Helicobacter pylori* can lead to chronic inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) and increase the risk of most gastric cancers and colorectal cancer, tobacco smoking leads to chronic airway irritation and inflammation and can promote lung cancer.

DEN primarily affects the liver and can damage intracellular organelles like mitochondria, endoplasmic reticulum and cause hepatocyte death (Cayama *et al*., 1978; Lim, 2002; Karin, 2006; Hadem *et al*., 2014; 2016; Basaiawmoit *et al*., 2016). DEN induced hepatocellular carcinoma (HCC) arise due to an exchange of inflammatory signals between dying hepatocytes and myeloid cells. The dying hepatocytes release byproducts such as HMGB1, interleukin-1 alpha (IL-1α) which causes activation of Kuffer cells (Scaffidi *et al*., 2002; Sakurai *et al*., 2008). Rapid accumulation of TNF-α was seen upon administration of DEN (Maeda *et al*., 2005) and the process of carcinogenesis is mainly associated with the release of this cytokine (Sethi *et al*., 2008; Balkwill, 2009). Inflammation has been regarded as the 'seventh hallmark of cancer' and key mediator between the two is TNF-α (Mantovani *et al*., 2008; Mantovani, 2009).

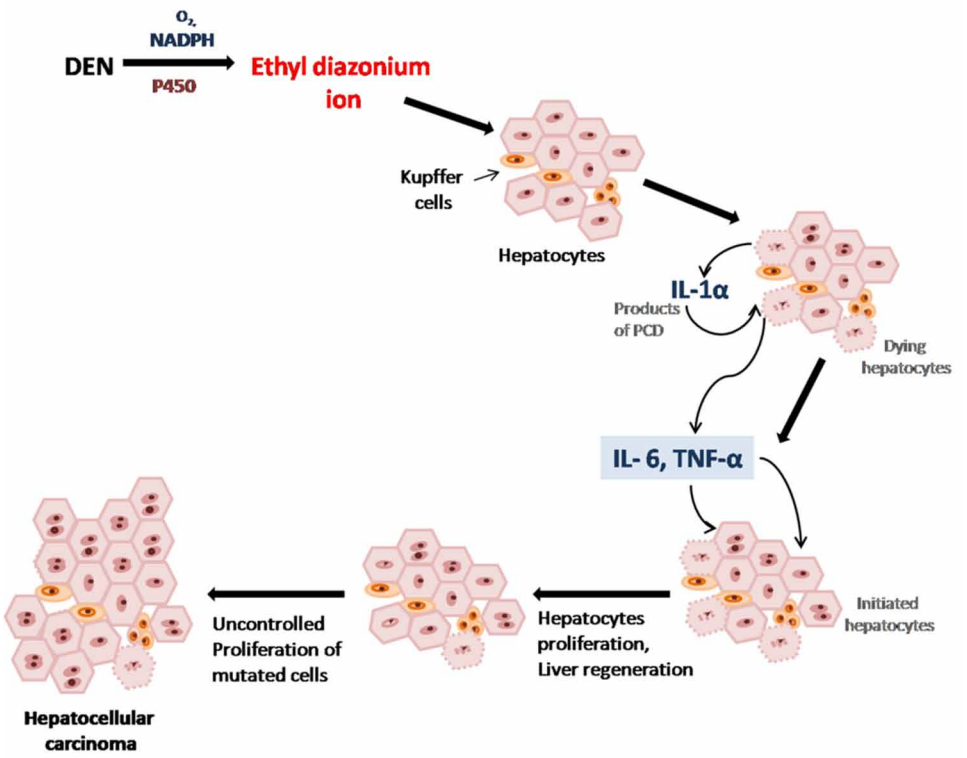
INFLAMMATORY CYTOKINE TUMOUR NECROSIS FACTOR α (TNF-α) IN CARCINOGENESIS

TNF-α is a proinflammatory cytokine with a molecular weight of 17 kDa. In humans, TNF-α is expressed as a 27-kDa protein that is proteolytically cleaved by a metalloprotease TNF α-converting enzyme (TACE), resulting in a 17-kDa molecule (Black *et al*., 1997). They are released mainly from activated macrophages, astroglia, microglia, Langerhans cells, and Kupffer cells though it is also produced by many different types of cells in the body. TNF belongs to the TNF/TNFR superfamilies that are involved in signalling pathways for cell proliferation, survival and differentiation and TNF-α is reported to play a role in many clinical conditions (Beutler 1993, Higashi *et al*., 1995, Risberg *et al*., 1991, Strieter *et al*., 1993, Licinio and Wong, 1996, Cressman *et al*., 1996, Muller-Ladner, 1996).

Various experimental studies carried out on different models by Kitagawa *et al*. (1984), Komori *et al*. (1993), Fujiki & Suganuma (1994), Sueoka *et al*. (1997), strongly indicate that TNF-α is an endogenous carcinogenic inflammatory cytokine. Independent studies carried out by Kishimoto (1989) and Suganuma *et al.* (2002), found that the signaling sequence in carcinogenesis is initiated from TNF-α through IL-1 to IL-6 and back to TNF- α, suggesting that TNF- α is the master cytokine in tumor promotion. TNF-α is involved in different stages of carcinogenesis right from initiation by inducing genetic changes in the cells, (Komori *et al*., 1993, Suganuma *et al*., 2002) metastasis by stimulating certain chemokines, such as CXCL1 and CXCL2 (Acharyya *et al*., 2012) and more significantly in progression through the activation of NF-κB transcription factor which is required for gene expression of TNF-α and other proinflammatory cytokines (Sen & Baltimore, 1986).

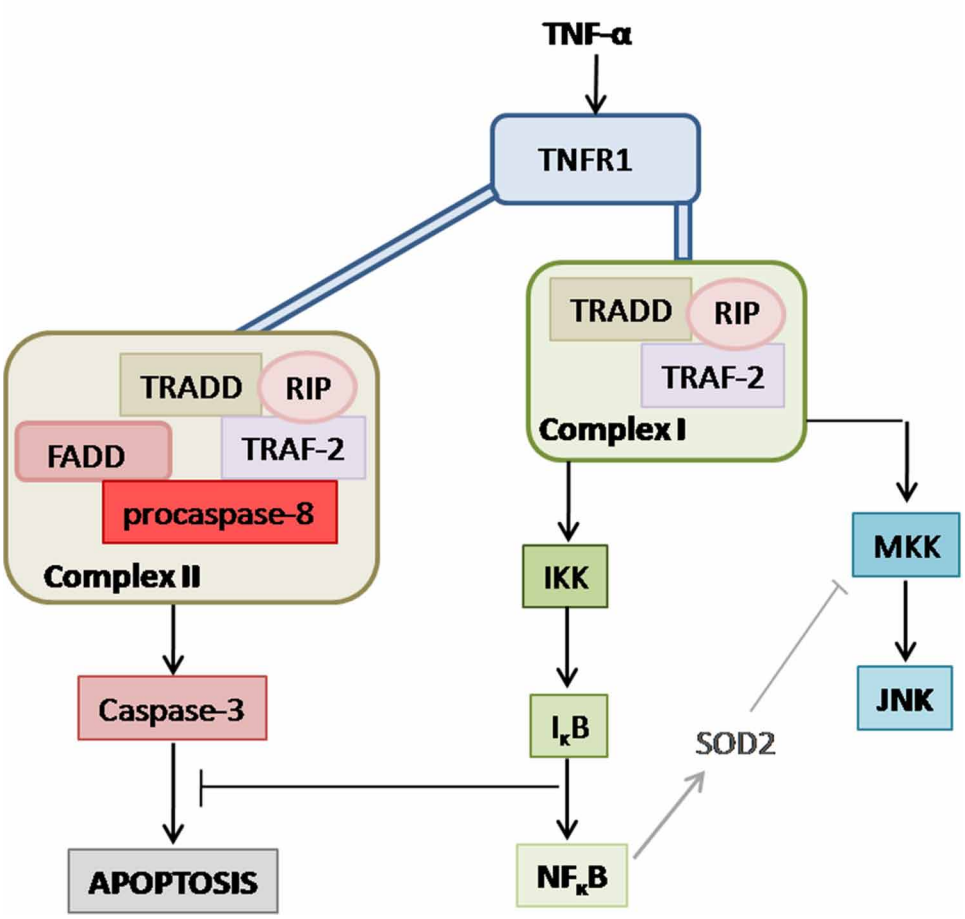
Depending on the cell type there are different signalling mediators involved for TNF-α induced signaling pathway. The binding of TNF to its receptor can induce either cell survival or cell death. There are more than 20 members of TNFR family categorized into two broad groups based on the presence

Figure 3. Exposure to DEN activates specific intracellular programmes to induce programme cell death (PCD). Compensatory proliferation of hepatocytes occurs to maintain liver integrety which can lead to the development of HCC. (Source: Papa et al., 2009).



or absence of a death domain. The traditional TNF signal cascade starts with the binding of TNF-α to TNFR1 (p55, p60, CD120a) and the recruitment of TNF receptor associated death domain (TRADD), TNF receptor associated factor 2 (TRAF2), and receptor interacting protein (RIP 1) to form complex I. Complex I can activate mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases (ERK), and c-Jun N-terminal kinases (JNK) which in turn activates activated protein 1 (AP-1), complex I can also activate NF-κB (Sen and Baltimore, 1986; Westwick *et al*., 1994; Karin 1995; Karin *et al*., 1997). TNFR1 (p55, p60, CD120a) and Fas (Apo-1, CD95) recruits TRADD, Fas-associated death domain protein (FADD) and procaspase-8 to form complex II which activates several effector caspases that are responsible for apoptosis (Boldin *et al*., 1995; Chinnaiyan *et al*., 1995; Ashkenazi & Dixit, 1998; Rathmell & Thompson, 1999) (Figure 32.4). Recruitment of TRAF2 by other TNF receptor (TNFR)-related members like TNFR2 (p75, p80), CD30 and Ox40 also regulates NF-κB and AP-1(Rothe *et al*., 1994; 1995; Gedrich *et al*., 1996; Arch & Thompson, 1998; Arch *et al*., 1998). Activation of transcription factors NF-κB and AP-1 has been linked directly to cellular proliferation, survival and differentiation (Arch & Thompson, 1999; Locksley *et al*., 2001).

Figure 4. TNF-α signalling pathway for induced cell death programme and proliferation. (Source: Papa et al. 2009).

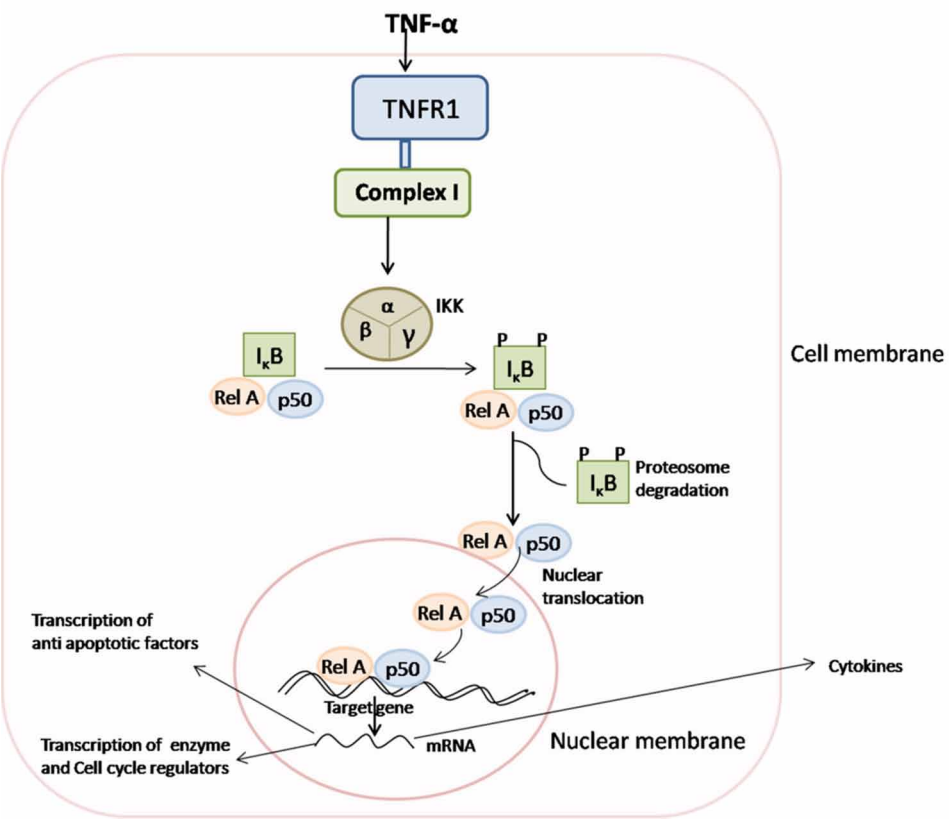


NF-κB TRANSCRIPTION FACTORS SIGNALLING IN CELL PROLIFERATION

NF-κB group of transcription factors plays a crucial role in development, cell survival and are known to be coordinators of inflammation and innate immunity (Hayden & Ghosh, 2004; Dutta *et al*., 2006). These transcription factors recognise the κB motifs of DNA. NF-κB consists of homo and heterodimers which composed of p50, p52, p65 and c-Rel. p50-p65 heterodimer also known as Rel A is the most prominent form of NF-κB (Ghosh & Karim, 2002). Inhibitory $I_\kappa B$ proteins are directly associated with NF-κB dimers and hold them in an inactive state in the cytoplasm. $I_\kappa B$ kinase (IKK) complex consisting of the regulatory subunit IKK-γ and two catalytic subunits IKK-α and IKK-β can phosphorylate $I_\kappa B$. Phosphorylation of $I_\kappa B$ leads to its poly-ubiquitination and subsequent proteolytic degradation, liberating NF-κB dimers to enter the nucleus and initiate transcription of genes with κB sites (Figure 32.5). Although both catalytic IKK subunits are capable of inducing $I_\kappa B$ phosphorylation, IKK-β is a more efficient $I_\kappa B$ kinase than IKK-α, IKK-β mediates the majority of $I_\kappa B$ phosphorylation *in vivo* (Ghosh & Karim, 2002).

NF-κB activation is observed in many forms of cancer. Activated NF-κB is constitutively expressed in tumour cells from breast, colon, blood neoplasm, pancreas and squamous cell carcinoma cell lines

Figure 5. NF-κB transcription factors activation in response to inflammatory cytokines. (Source: Scott & Roifman, 2019 with modification).



(Kaltschmidt & Kaltschmidt, 2003). NF-κB plays an important role in tumour promotion since it is the major activator of anti-apoptotic gene expression. NF-κB was shown to be instrumental in tumour promotion in a colitis-associated cancer (CAC) model. NF-κB promotes production of cytokine IL-6 in myeloid cells that act as growth promoters for the pre-neoplastic enterocytes whereas in enterocytes NF-κB activates anti apoptotic genes leading to proliferation of pre-malignant cells (Greten *et al*., 2004). Pikarsky *et al*., (2004) study of hepatocellular carcinoma (HCC) in multidrug resistance 2 (*Mdr2*)-knockout mice showed that NF-κB activation in heptocytes suppresses apoptosis of pre-malignant cells and it is an inflammation-induced phenomenon secondary to parenchymal infiltration by inflammatory cells (Kupffer cells). NF-kB activation is primarily induced by TNF-α through paracrine stimulation. NF-κB is essential for tumour promotion and regulates multiple anti-apoptotic genes including cellular inhibitors of apoptosis (cIAPs), caspase-8 inhibitor c-FLIP, members of the Bcl-2 family, A1/Bfl-1, Bcl-xl, TRAF2 and the zinc finger protein A20. Some act by either blocking the activity of death receptors or the mitochondrial death pathway (Wajant *et al*., 2003). The crosstalk between the NF-κB and JNK pathways is another mechanism by which NF-κB protects hepatocytes from TNF-α induced cell death. NF-κB regulates transcription factors X-liked inhibitor of apoptosis (XIAP) and Growth arrest DNA damage-inducible gene 45β (GADD45) as well as the antioxidant enzyme SOD2 that are linked to the repression of JNK activity. NF-κB thus provides a connection between its activation and subsequent

suppression of ROS and tumour promotion and progression in TNF-α induced cell death (De *et al*., 2001; Tang *et al*., 2001).

In the studies conducted by Maeda *et al*. (2005) Naugler *et al*. (2007) and Sakurai *et al*. (2008), where they used DEN to induce HCC in mice, hepatocarcinogenesis occurs through the production of cytokine that stimulates compensatory proliferation. Administration of DEN caused rapid accumulation of ROS and elevated oxidative stress which mainly affects centrilobular (zone 3) hepatocytes where DEN is metabolized (Yang *et al*., 1990). ROS accumulation caused hepatocyte death which results in the release of IL-1α and other substances such as HMGB1, S100 calcium-binding proteins, purine metabolites or heat-shock proteins from the dying cells (Karin & Greten, 2005). These substances caused activation of Kupffer cells which induces rapid production of TNF-α and IL-6 and hepatocyte growth factor (HGF) by stellate cells whose production depends on factors produced by Kupffer cells. TNF-α/IL-6 induced program cell death (PCD) in hepatocytes but since the liver can regenerate due to its remarkable proliferative capacity, elevated hepatocyte death enhances compensatory proliferation and survival of genetically altered cells. ROS accumulation also leads to JNK1 activation and c-jun expression. JNK1 activation further contributes to ROS accumulation. JNK and c-jun are important contributors to hepatocyte proliferation and HCC development. Activation of NF-κB and AP-1 dependent via TNF-α stimulation thus leads to cell proliferation (Papa *et al*., 2009).

PHYTOCHEMICAL-BASED ANTICANCER DRUG DEVELOPMENT FROM PLANTS WITH EMPHASIS TO CANCER

Natural products are a source of new drugs and about 80% of drugs are from natural products or their derivatives. Many areas of scientific specialization including botanical, phytochemical, biological, molecular techniques, pharmacology and high-throughput screening (HTS) are involved in drug discovery from medicinal plants (Balunas & Kinghorn, 2005; Wassermann *et al*., 2015). Since the 1940s to date, of the 175 small molecules, 85 or 48.6% are either natural products or directly derived from them are approved anticancer agents (Newman & Cragg, 2016). Anticancer agents derived from plants currently in clinical use are camptothecin (CPT), vinblastine, epipodophyllotoxins, taxanes, camptothecins, combretastatins and homoharringtonine (Balunas & Kinghorn, 2005; Cragg & Pezzuto, 2016). These plant derived natural products can be classified into the following chemical groups: Aldehydes, Alkaloids, Annonaceous acetogenins, Polyphenols (flavonoids and phenolics), Glycosides, Lignans, Lipids, Lipids (unsaponified), Nucleic acids, Polysaccharides, Proteins, Terpenoids. These phytochemicals exert their anticarcinogenic effects by different mechanisms. Several alkaloids exhibit antiproliferation and antimetastasis effects on various types of cancers both *in vitro* and *in vivo* (Lu *et al*., 2012). Elimination of carcinogenic compounds by activating detoxifying enzymes is one way to prevent carcinogenesis and many compounds like Glucosinolates and indoles, thiocyanates and isothiocyanates, phenols and coumarins have been shown to play an important role in detoxification process (Keck & Finley, 2004). Activation of nitrosamines into their highly reactive forms is blocked by ascorbate and phenols (Mirvish, 1981; Bartsch & Frank, 1996). Flavonoids and phenolic act as free radical scavengers and metal chelators depending on their chemical structures. They act as antioxidants to reduce the oxidative stress produced by some carcinogens, therefore improving cell survival (Rice *et al*., 1995; García *et al*., 2018) or they can act as prooxidants inducing apoptosis and blocking cell proliferation. Flavonoids inhibit tumor growth by inducing apoptosis of transformed cells; prevent angiogenesis and metastasis (Wenzel *et al*., 2000).

Dietary polyphenols contribute to the prevention of cancer onset and development (Yao *et al*., 2004; Porrini *et al*., 2005). Polyphenols can directly interact with specific steps and/or proteins responsible for the regulation of apoptotic process such as the release of cytochrome *c* with subsequent activation of caspases-9 and caspases-3 (Yao *et al*., 2004; Porrini *et al*., 2005), the increase of caspases-8 and t-Bid levels, the down-regulation of Bcl-2 and Bcl-XL expression, the enhanced expression of Bax and Bak (Kuo & Lin, 2003; Lee *et al*., 2005; Selvendiran *et al*., 2006) and the modulation of nuclear factor NF-κB (Gong *et al*., 2003). Polyphenols also exhibit chemosensitizing, radiosensitizing, and radioprotective activities (Jagetia *et al*., 2008).

ARISTOLOCHIA TAGALA AND *CURCUMA CAESIA* MITIGATES THE EFFECT OF DIETHYLNITROSAMINE IN MICE

Aristolochia tagala Cham. (AT) known as Khur thlong in the Khasi dialect belonging to the family Aristolochiaceae is widely distributed in India, Sri Lanka, China, Malaysia, Burma, Java, and Australia (Murugan *et al*., 2006). It is one of the important medicinal plants found in Meghalaya which is part of the Indo-Burma biodiversity hotspot and is used by the people of this region for primary health care (Tandon *et al*., 2008; Singh, 2010). The roots of this plant are used by herbal practitioners for a wide range of disorders. Different parts of *A. tagala* have been reported to have antimicrobial propertities, inhibit cell proliferation, as insecticides, as pain modulators (Dey & De 2012; Latha *et al*., 2015). Some phytochemicals and compounds have been identified from this plant with potential pharmacological activities (Deepaa *et al*., 2010; Battu *et al*., 2011; Remya *et al*., 2016; Hadem & Sen 2018a; 2018b). The anticancer/antitumor activity of *A. tagala* has also been reported by Angeles *et al*. (1970), Garg *et al*. (2007) against KB and Anilkumar *et al*. (2014) against different cancer cell lines.

Curcuma caesia Roxb. (CC), commonly known as black turmeric due to the bluish black colour of the rhizome is widely found in the Himalayan region, Northeast, and Central India. The ethanomedical uses of *C. caesia* was for the treatment of cough, asthma, wounds, inflammation, stomachache, dysentery, fever, etc. (Kala, 2005; Basak *et al*., 2010; Pfoze *et al*., 2012;). *C. caesia* has a wide range of biological and pharmacological activity. It is reported to have anti-asthmatic, neuropharmacological, antidepressant, antiulcer, nephroprotective, antimutagenic, thrombolytic activities (Arulmozhi *et al*., 2006; Karmakar *et al*., 2011a; 2011b; Bordoloi *et al.*, 2012; Maurya *et al.*, 2014; Devi *et al*., 2015; Fathima *et al*., 2015) and have shown to possess high antioxidant properties (Dhal *et al.*, 2012; Reenu *et al*., 2015). *Curcuma caesia* contains many essential oil and compounds with biological property (Mukunthan *et al*., 2014; Chaturvedi *et al*., 2019; Al-Amin *et al*., 2019; Kumar *et al*., 2020). Essential oil from the leaves of *C. caesia* was shown to possess antibacterial properties against *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus* and *Salmonella typhimurium*; and antifungal effect against *Aspergillus fumigatus*, *Aspergillus niger*, *Saccharomyces cerevisiae* and *Candida albicans* (Borah *et al*., 2019). The anti-cancer activity of *C. caesia* was evaluated in different human cancer cell lines. It was reported to have anti-proliferative activity against (MCF-7) human breast cancer, (HCT-116) human colon cancer, (PA-1) ovarian cancer and (DU-145) prostate cancer (Shaikh *et al*., 2016; Liu *et al*., 2013). The antitumor activity of *C. caesia* was also reported against Ehrlich's ascites carcinoma (EAC)-treated mice. The compound curcuzederone isolated from the rhizomes of the plant was found to inhibit migration of MDA-MB-231 cell line (Al-Amin *et al*., 2019).

Figure 6. Aristolochia tagala and Curcuma caesia in their natural habitat.

From the study conducted by the authors, the anticancer property of *A. tagala* and *C. caesia* in DEN induced HCC of mice was evident morphologically where the plants was able to reduce the number of preneoplastic nodules formed when the animals were administered with DEN for prolonged period of 16-28 weeks. Structural change such as irregular cell shape, irregular nuclear shape and fragmented nuclei which were observed in H&E liver sections of DEN induced mice were reduced in liver section of animals treated with plant extracts of *A. tagala* and *C. caesia* (Hadem *et al*., 2014). The elevated activity of marker enzymes such as AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phospatase) and AChE (Acetylcholine esterase) caused by DEN induction was attenuated by the plant extracts (Hadem *et al*., 2014). Relatively, the protective effect *C. caesia* was more consistent than *A. tagala*. These enzymes are markers in diagnosis of liver injury and functional integrity of the membrane and in HCC since they are expressed by most tumors and rapidly dividing cells (Plaa &Hewitt, 1989; Frederiks *et al*., 1990; Zakut *et al*., 1990; Soreq *et al*., 1991; Tarao *et al*., 1999). Lipid peroxidation and membrane damage caused by DEN resulted in the liberation of these enzymes into serum. *C. caesia* and *A. tagala* might have been able to reduce the effect of DEN by protecting membrane integrity thereby decreasing enzyme leakage.

DEN-induced inflammatory response seen by an increase in TNF-α level was reduced by treatment with the extracts of both plants. Maeda *et al*. (2005) and others also reported that there was a rapid accumulation of TNF-α upon DEN administration. As mentioned, DEN was known to primarily affect liver tissue and cause hepatocyte death (Cayama *et al*., 1978; Lim, 2002; Karin, 2006). Kupffer cells activation by products such as HMGB1 and IL 1-α released by dying hepatocytes is a well-established proinflammatory mechanism (Scaffidi *et al*., 2002; Maeda *et al*., 2005; Naugler *et al*., 2007; Sakurai *et*

al., 2008). An inflammatory signalling between dying hepatocytes and myeloid cells is a mechanism that initiates cell proliferation and HCC development. Various studies have associated TNF-α with cell proliferation, e.g. hepatocyte proliferation and liver regeneration after partial hepatectomy was prevented by administration of TNF-α antibody (Ankerman *et al*., 1992). Chemically induced skin cancers develop fewer experimental metastases in TNF-α/TNF-α receptors-deficient mice. A marked reduction in tumour onset and tumour burden was seen upon inhibition of TNF-α (Karin & Greten, 2005).

The downstream signalling cascade of TNF-α to NF-κB is essential for tumour promotion and progression since NF-κB is the major activator of anti-apoptotic gene expression and pro survival genes. In DEN induced model, activation of IKKβ/NF-κB in Kupffer cells promotes tumour development through the production of inñammatory cytokines and growth factors that signals rapid multiplication of surviving hepatocytes with DNA damages to balance the loss cell mass. Indeed, administration of DEN was found to increase the NF-κB activity and this increase was further elevated on prolonged exposure of 28 weeks. There is a correlation between increase NF-κB activity and the levels of TNF-α. TNF-α secreted from stromal cells may have been responsible for NF-κB activation, to stimulate proliferation of surviving hepatocytes. Mice treated with *C. caesia* or *A. tagala* attenuates the effect of DEN on NF-κB activity maybe by lowering inflammation, reduced TNF-α level which subsequently reduce NF-κB activation. At a shorter treatment period of 16 weeks, the inflammation did not subside considerably upon treatment with *C. caesia* but somehow, NF-κB activation was prevented more efficiently. This suggested that *C. caesia* may be able to inhibit activation of NF-κB directly.

The phytochemical constituents present in *A. tagala* are flavonoids, phenolics, steroids and tannins that in *C. caesia* are alkaloids, flavonoids, phenolics, steroids, tannins and terpenoids. Both plants contain high phenolic content but the flavonoid content was higher in *A. tagala* (Hadem *et al*., 2016). Separation of these phytochemical by column chromatography afforded three fractions from *A. tagala* and five fractions from *C. caesia*. The free radical scavenging potential of *C. caesia* crude extract and the fractions was higher than *A. tagala*. This may be due to the additional presence of terpenoids besides phenolics and flavonoids which are present in *A. tagala* and also the compounds maybe in bound or polymerized forms, which can only be released through hydrolysis. Compounds like Catechol or hydroquinone and terpenoids may be present in *C. caesia* while flavonoids, anthocynidin 3-glycosides and 6-hydroxylated flavonols as well as some flavones and chalcone glycosides may be present in *A. tagala* as indicated by High Performance Thin Layer Chromatography (HPTLC) analysis (Hadem *et al*., 2016).

The mechanism by which DEN induce HCC in mice is by the generation of electrophilic ethyldiazonium ions upon metabolic activation of the carcinogen. These highly reactive ions interact with DNA, proteins and lipids causing a chain reaction leading to increasing ROS pool. Accumulation of ROS leads to oxidative stress and hepatocyte death and eventually compensatory proliferation involving many signalling cascades. The ability of these plants to reduce the effect of DEN and subsequently HCC was thought to be due to their ability to scavenge ROS generated thereby reducing the load and/or sources of ROS. Phenolics and flavonoids are known to have excellent antioxidant activity, while terpenoids, alkaloids have shown to have moderate antioxidant activity (Kasote *et al*., 2015). Phenolics and flavonoids like Caffeoylquinic acid, Kaempferol, apigenin dimethyl ether, as well as other compounds like Aristolone, Magnoflorine, N-Trans-Feruloyldopamine, β-sitosterol and Stigmasterol present in *A. tagala* (Hadem & Sen 2018a; 2018b) and known to have antioxidant property may have contributed to the antioxidant property of *A. tagala* (Yoshida & Niki 2003; Hung *et al*., 2007; Wang 2010; Li *et al*., 2014; Krishna *et al*., 2015; Dizdar 2018). Besides phenolics and flavonoids present in *C. caesia*, terpenoids may be an important contributing factor to their antioxidant property. Ar-turmerone, Borneol, 1,8-cineole, Linalool

present in *C. caesia* have been reported to have antioxidant activity and are potent inducers of detoxifying enzymes, thereby reducing oxidative damage (Kumar *et al*., 2010; Ciftci *et al*., 2011; Liju *et al*., 20011; Seol *et al*. 2016). Besides antioxidant activity many of these compounds also have anti-inflammatory activity. Considering the role that ROS plays in initiating inflammatory response, the mechanism by which these plants showed anti-inflammatory activity is also because of their antioxidant activity.

CONCLUSION

From various reports and our observations, the two plants *A. tagala* and *C. caesia* exhibited potential anticancer properties. They possessed antioxidant, antiinflammatory and antiproliferative properties. The mechanism by which they exert anticancer effects in DEN induced HCC was through TNF-α mediated decrease NF-κB binding activity. Natural product research is an area that is essential for effective drug discovery and development and medicinal plants is one source that is abundant and replenishing. The two plants are important source of drug development since they contain a number of compounds with biological activity that can be extracted and isolated for therapeutic used.

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Chapter 20
Essential Oils and Their Biological Applications:
Extraction methods, Types, Biological Activities, Antimicrobial Fumes

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ABSTRACT

Essential oils are terpinoids and their oxygenated derivatives, which are widely used for antimicrobial, fungicidal, antiparasitical, insecticidal uses. They are aromatic, hydrophobic, and volatile in nature and frequently used in medicinal and cosmetic industries. Especially nowadays, volatile oils have a significant role in pharmaceutical, sanitary, cosmetic, agricultural, and food industries. Various conventional and modern methods of extraction of volatile oil are available. Volatile oil can play an important role in minimization of microbial load at primary stage and/or to prevent the growth of the microorganisms during various stages of product management. However, there is still the need more emphasis on research regarding EO.

INTRODUCTION

Medicinal aromatic plant is a general term which is commonly used to refer spices, condiments, perfumes and flavoring agents. These aromatic plants consist of essential oil (EO) or volatile oils due to which they produce specific flavors or odors and used as spices or perfumery agents. Essential oils (EOs) are natural, highly volatile, aromatic, hydrophobic liquid and compounded mixtures of low-molecular-weight usually obtained in plants and used in ancient time for medicinal and health motive (Mahato *et al.,* 2019). EOs formed as secondary metabolites in aromatic plants as in reaction to attacks by herbivores, insects, microorganism, and other entities (Raut & Karuppayil, 2014). Due to their volatile nature they can be easily extract out by the steam distillation method from different natural sources (Mahato *et al.,* 2019)

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and their antidepressant, detoxifying, stimulating, antimicrobial, and calming effects, EO gain huge admiration as a natural, secure an efficient therapy for health problems (Tongnuanchan & Benjakul, 2014). EOs are complex, comprises of various chemicals, mostly present in liquid state but very few in solid form also. At normal temperature, these volatile oils may appear colorless to light yellowish in color and are readily absorbed through the skin. EO usually have lower density then water but few volatile oils like cinnamon oil, clove oil, etc. possesses high density than water. They are miscible in vegetable oils, fats, wax, and water and also soluble in diethyl ether, acetone, ethyl acetate, ethanol (Solórzano-Santos & Miranda-Novales, 2012). EOs of same plant may differ completely in aroma and properties from part to part e.g. Geranium plant yields oil from flowers and the leaves, and both oils from different parts differ in constituents, aroma and other properties (Veras *et al.,* 2012; Rivera Calo *et al.,* 2015). In plants, generally volatile oil stored in glands, oil ducts, resin ducts, or glandular trichomes of the plants. The quality of EOs usually affected by various interlinked factors, such as climatic conditions, seasonal and geographical conditions, harvesting time and method of extraction (Pannizi *et al.,* 1993). The oils yield from the various parts of plants could be pretentious at the various stages of the plant growth. EOs is generally used as flavoring ingredient such as in edible products, drinks, perfume industries, pharmaceuticals, and cosmetics manufacturing.

Various compositions of EO make it potential to use them as potent antimicrobial agent with a low risk of microbial resistance occurrence (Bakkali *et al.,* 2008).

NATURAL SOURCES OF ESSENTIAL OILS

Around 3000 EOs is known till date, of which only 300 EOs are commercially valuable. Most of the EOs is used in pharmaceuticals, sanitary, food, cosmetic, and perfume industries (Bakkali *et al.,* 2008). Plants producing EOs belongs to around 60 families which includes, Lamiaceae Alliaceae, Apiaceae, Myrtaceae, Asteraceae, Poaceae, and Rutaceae (Carson *et al.,* 2006). They may be originate in individual portions of the plant such as leaves (mint), flower (rose), peel (orange), seed (Basil) berries (juniper), rhizome (ginger, turmeric) bulb (garlic), root (jatamansi), bark (cinnamon), wood (sandal wood), resin (frankincense), petals (marigold), etc. (Pannizi *et al.,* 1993)

COMPONENTS OF ESSENTIAL OILS

EO is the mixture of various phytochemicals and obtained from the primary metabolites in the form of secondary metabolites. EO is present in high concentration (approximately 20-70%) (Croteau *et al.,* 2000; Betts, 2001). Numerous compounds which belong from the family of terpenes have been recognized in EOs. Majority of EO components alone show the biological properties (Veras *et al.,* 2012) but occasionally a combination of molecules changes biological activity (Carson *et al.,* 2006; Bakkali *et al.,* 2008). The EO constituents of any specific plant depends on the plant part used, whether it be flowers, leaves, stems, bark, wood, whole fruits, pericarp, seed, or roots (Rivera Calo *et al.,* 2015).

Terpenoids and Phenylpropanoids originates by diverse precursors of the primary metabolism and are synthesized by dispersed metabolic pathways and they are further classified into different groups, such as functionalized derivatives of alcohols (geraniol, α-bisabolol), ketones (menthone, p-vetivone), aldehydes (citronellal, sinensal), esters (γ-tepinyl acetate, cedryl acetate), and phenols (thymol) (Başer

et al, 2007; Tabanca, 2007). EOs also contains non-terpenic composites biogenerated via the Phenylpropanoids pathway, such as eugenol, cinnamaldehyde, and safrole (Modzelewska, 2005).

TYPES OF ESSENTIAL OILS

Essential oils are classified into two chemical groups (1) Terpenoids and (2) Phenylpropanoids

Terpenoids

Terpenoids are naturally occurring hydrocarbons and basically consist of five carbon isoprene units. Terpenoids are the terpenes obtained from the several kinds of plants and flowers in the form of primary constituents of the EOs (Thimmappa, 2014). Within terpenoids; monoterpenoid and sesquiterpenoid families are main because majority of most important components of EOs found in the plants (Ludwiczuk, 2017). Terpenoids are divided into hemeterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), triterpenes (C_{30}) and tetraterpenes (C_{40}) depending on its carbon units although monoterpenes (C_{10}) and sesquiterpenes (C_{15}) are the major terpenoids (Bakkali *et al.,* 2008).

Various Examples of EOs are turpentine, α and β-pinene isolated from Pinus species, geraniol isolated from *Rosa damascena*, terpinen-4-ol from *Melaleuca alternifolia* (tea tree oil), linalool from *Coriandrum sativum*, zingiberol from *Zingiber officinale* and cineol from *Eucalyptus globulus*, etc. (Bakkali *et al,* 2008; Sell, 2010; Chamorro *et al.,* 2012).

Hemiterpenes

Hemiterpene are the type of terpene having C_5 atom and formed from a single isoprene unit. Molecular formula is C_5H_8. Eucalyptol, citronellol, limonene, humulene and Forskolin are the example of hemiterpene. These type of compounds used as a flavors, fragrances, food additives and pharmaceuticals and possess various biological properties (Semih & Vasfiye, 2021).

Monoterpenes

Biosynthetically monoterpenes are synthesized from units of isopentenyl pyrophosphate, which is made from acetyl-CoA via the intermediacy of mevalonic acid in HMG-CoA reductase pathway. The molecular formula of monoterpenes is $C_{10}H_{16}$ and comes under the class of terpenes and consists of two isoprene units. Monoterpenoids are characterized by oxygen-containing functional groups. Structural isomers-acyclic (myrcene and ocimene are the type of acyclic monoterpene), monocyclic (α terpineol, limonene, thymol, menthol, carvone, eucalyptol, and perillaldehyde are the type of monocyclic monoterpene), and bicyclic monoterpenes (Carene, sabinene, camphene, and thujene are the type of bicyclic monoterpenes) (Ajikumar *et al.,* 2008). Geraniol, terpineol, limonene, myrcene, linalool or pinene is the examples of monoterpenes (Breitmaier, 2006).

Sesquiterpenes and Oxygenated Compounds

Biosynthetically sesquiterpenes are derived from farnesyl diphosphate by different enzyme-catalyzed cyclization reactions and rearrangements of carbon skeleton. Mono, bi and tricyclic forms of sesquiterpenes are commonly found in EOs in plants and shown wide range of biological activities (Merfort, 2011). Sesquiterepene molecular formula is $C_{15}H_{24}$. Chamazulene is found in German chamomile and has a pharmacological action (Safayhi *et al.,* 1994). Oxygenated functional group is found in EOs are the most common type group. The α-bisabolene and β-caryophyllene are the example of sesquiterpene (Swamy *et al.*, 2015).

Diterpenes

Biosynthetically diterpenes are derived from Geranyl geranyl pyrophosphate via the HMG-CoA reductase pathway with being a primary intermediate by plants, animals and fungi. Diterpenes belongs to the class of chemical compounds and molecular formula of diterpene is $C_{20}H_{32}$ and composed of four isoprene units Retinol, retinal, and phytol are the biologically active diterpenes compounds and they give anti-inflammatory and antimicrobial activity (Breitmaier, 2006; Davis *et al.*, 2000).

Triterpene

Triterpenes structurally large diverse group of natural compounds and biogenetically derived from active isoprene unit. Biosynthesized by the condensation of two farnesyl diphosphate (FPP) units followed via reduction (Dewar *et al.*, 1987). Triterpenes consist of the C_{30} class of isoprenoids and the molecular formula $C_{30}H_{48}$. Triterpenes represent secondary metabolites, especially pentacyclic ones and extensively dispersed in the plant kingdom and originate in leaves, stem bark, fruits and roots (Jäger *et al.*, 2009). Oleanane, ursane, taraxerane, taraxastane, lupane, and tetracyclic-dammarane and cucurbitan are the example of triterpene (Sticher, 2010).

Tetraterpene

Tetraterpenes are made up of two (C_{20}) geranylgeranyl disphosphates in a head-to head condensation reaction. Tetraterpene compounds made up of eight isoprene unit and belong to the class of carotenoids and have a molecular formula $C_{40}H_{64}$ (Davis *et al.*, 2000). Caratenoids includes Lycopene, β-carotene, and lutein are the example of tetraterpenoids and have a good antioxidant property (Dall'Osto *et al.*, 2012).

Phenylpropanoids

The most frequently investigated metabolic route is phenylpropanoid pathway, among secondary metabolites. The phenylpropanoids are synthesized by plants from the amino acids phenylalanine and tyrosine and they are diverse family of organic compounds (Barros *et al.*, 2016). In EOs aromatic compounds are present and usually derived from phenylpropane, and they are in lower concentration than terpenes. Various examples of Phenylpropanoid EOs such as, aniseed from *Pimpinella anisum*, star anise from *Illicium verum*, and fennel from *Foeniculum vulgare*, all with trans-anethol; cinnamon from *Cinnamomum*

Table 1. List of various types of terpenoids and characteristic features

Terpenoids	Isoprene unit	Carbon atoms	Molecular formula	Examples of different terpenoids	Reference(s)
Hemiterpenes	1	(C5)	C_5H_8	Eucalyptol, citronellol, limonene, humulen, Forskolin etc.	Semih *et al.,* (2021)
Monoterpene	2	(C10)	$C_{10}H_{16}$	geraniol, terpineol, limonene, myrcene etc.	Breitmaier, (2006)
Sesqueterpene	3	(C15)	$C_{15}H_{24}$	α-bisabolene, β-caryophyllene etc	Swamy *et al.*, (2015)
Diterpene	4	(C20)	$C_{20}H_{32}$	Retinol, retinal, phytol etc.	Breitmaier, (2006); Davis *et al.*, (2000)
Triterpene	6	(C30)	$C_{30}H_{48}$	oleanane, ursane, taraxerane, taraxastane, lupine etc.	Sticher, (2010)
Tetraterpene	8	(C40)	$C_{40}H_{64}$	Lycopene, β-carotene, lutein etc	Dall'Osto *et al.*, (2012)

verum with trans-cinnamic aldehyde; and Eugenol from *Eugenia caryophyllus* (Bakkali *et al.*, 2008; Sell, 2010; Chamorro *et al.*, 2012).

Derivatives of terpenes

Alcohol

Alcohols are most common EOs and are the very useful molecules in aromatherapy. There are two types of alcohol they gives a better biological activity. Terpene alcohols stimulate the immune system, diuretic and anti-bacterial activity. Linalol extracted from rosewood and lavender, Citronellol extracted from rose, lemon, eucalyptus and geranium. Geraniol may be extracted in geranium and palmarosa, Farnesol found from chamommile. Other terpene alcohols include borneol, menthol, nerol, terpineol, vetiverol, benzyl alcohol, and cedrol are the examples of terpene alcohols. Sesquiterpene Alcohols are used as anti-inflammatory, antibacterial, anti-mycotic, and ulcer-protective property. A strongest sesquiterpene alcohol is Bisabolol and found in chamomile oils (Tisserand & Balacs, 1995).

Ester

The compound resulting from the reaction of an alcohol with an acid is called esterification and esters are found in a large number of EOs. Esters are generally non-toxic. Esters have an intensely fruity aroma. Linalyl acetate found from bergamot, Clary sage, and lavender and Geraniol acetate found in sweet marjoram. Bornyl acetate, eugenol acetate, and lavendulyl acetate are other esters. They have anti-inflammatory, anti-spasmodic, anti-fungal, calming (for physical body and nervous system) and relaxing property (Caddy, 1997).

Aldehyde

The aldehyde group (C-H-O) is highly reactive. When applied topically (citral being one example) they can be quite irritating and when inhaled may have a profound calming effect. Aldehydes elements have

also been found in lavender and myrrh. Citral and Citronellal is also very common and present in the oils of melissa, lemongrass, lemon, mandarin, lemon-scented eucalyptus, and citronella. benzaldehyde, cinnamic aldehyde, cuminic aldehyde, and perillaldehyde other aldehydes. Sedative effect on the central nervous system is common properties of aldehydes, antimicrobial, and antiinflammatory (Lawless, 1995).

Ketone

Sometimes constituents of ketons are mucolytic and neuro toxic. Ketones also excite cell regeneration, support the formation of tissue, and liquefy mucous. Ketone oils are useful in different conditions such as dry asthma, colds, flu and dry cough. Jasmone is present in jasmine and fenchone is present in fennel both are non-toxic in nature. Camphor, carvone, menthone, methyl nonyl ketone, and pinacamphone are other ketones (Price & Price, 2012).

Phenols

Phenols are chemically active with a distinct Fragrance. Phenols have good antiseptic, anti-bacterial, and antimicrobial property. They have also antioxidant property due to high contain of oxygenating molecules. Eugenol is found from clove and cinnamon oil, Thymol may be present in thyme. Carvacrol is present in oregano and savory. Methyl eugenol, methyl chavicol anethole, safrole, myristicin, and apiol are other phnelos (Clarke, 2008).

METHODS OF EXTRACTION OF ESSENTIAL OILS

EOs are valuable plant secondary metabolic products, generally composed of various volatile principles with aromatic characteristics (Brunteon, 1995). In oil glands, the EO droplets being stored or cavity which can be detached via either accelerate diffusion over the cell wall or through cell wall crushing. The extraction procedures for EO depend on the portion of the plant where the oil is to be extracted. The stability of the EO to heat and susceptibility of the oil constituents to change will also affect extraction method of oil. Various techniques used for the extraction of Essential oils are discuss below:

Conventional Extraction Methods

Hydrodistillation

Hydrodistillation is the oldest and easy method which is used for the extraction of EOs from plant materials. This method begins with immersion of the plant material into H_2O in the container and the mixture was boiled. The plant material from which oil is to be extracted and boiling water is in direct contact with each other (Rangari, 2017). The assembly for hydrodistillation includes a source of heat, vessel which contains water and plant material, a condenser which converts vapors produced into liquid, and a decanter. Decanter is used to collect the condensate and for separation of EO from water. In this technique extract plant materials is used to observe especially like wood or flower and the extractions which involve plant material whose boiling point is high. This method protects EOs to be extracted to a

certain extent without presence overheated because the oils are surrounded by water (El Asbahani *et al.*, 2009). Its main disadvantage is that complete isolation of oil is not possible (Rangari, 2017).

Steam Distillation

Steam Distillation is very popular technique used to extract and isolate EOs from plants. 93% of percentage yield of EOs extracted by this technique and the remaining oil can be extracted by using other methods. The method begins via heating the plant material by steam and the steam which is to be supplied is generated from steam generator. In this system packed bed of the plant is placed over the source of steam. The steam produced is passed through the plants (Masango, 2005). The steam vaporizes the volatile oil from the plant material which finally goes through the condensation and collection process. The apparatus used in this method is simple. This is an economical method of extraction. Volatile oil can be produced in large quantity with less human labor. As high pressure steam can cause decomposition of unstable perfume components, so distillation is best started with steam of low pressure followed by steam of higher pressure in the later stages of operation (Rangari, 2017).

Hydrodiffusion (HD)

The major difference between steam distillation and hydrodiffusion is that in steam distillation method, steam is supplied through the bottommost and in HD method; steam is supplied from the top. So this method is a sort of inverted steam distillation. The oil can be collected from the bottom. HD is started at low pressure and the temperature of steam can be declined below 100°C; so this technique is subjected only to samples that can be damaged at boiling temperature (Vian *et al.*, 2008). Oils with higher ester contents i.e. less thermally induced hydrolysis can be produced by this method. Microwave technology enhanced steam diffusion method (Bousbia *et al.,* 2009). HD method is better as comparison to steam distillation due to its low processing time and more yield with little steam used (Al-Shalah, *et al.,* 2020).

Solvent Extraction

The principle of this method is based on the dissolution of the components in the cells by the solvent (Fokou *et al.,* 2020). In this technique Solvents are use like acetone, petroleum ether, hexane, methanol, or ethanol. The plant material can be extracted by this method and which cannot be used heat or steam method for extraction (Tongnuanchan & Benjakul, 2014). In this process, the plant materials are mixed with solvents and mild heating is provided to the mixture. Then the mixture is filtered and evaporation of the solvent takes place. The filtrate contains a mixture of resin, wax, fragrance and EO. Alcohol is added in the filtrate to solubilize EO into it and after that it will be distilled at low temperature. In this method, the alcohol absorbs fragrance and is evaporated while the aromatic oil remains in the vessel. This method is very complicated as compared to other methods for EOs extraction that is why it is time-consuming and costly process (Li, *et al.,* 2009). Solvent extraction is used for plant materials that yield low amounts of EO, that are largely resinous, or for delicate aromatics which cannot tolerate the pressure and distress of steam distillation. This method also produces a finer fragrance than any type of distillation method.

Cold Pressing Method or Expression

The oils from the citrus peels obtained by distillation or any of the extraction process produce poor quality oil (Rangari, 2017). This method is used in the production of citrus oils. Mechanical extraction method oil is pressed in an expeller at low temperatures and pressure. The oil extracted by this process is 100% pure. This method is also known as scarification method (Arnould *et al.,* 1981). The outer most layers of the plants which consist of oil are removed. Then it is forced to squash out the material from the pulp and EO is released from the pouches. This type of EOs separated by centrifugation method and the released EO comes up on the surface of the material.

Enfleurage

It is classical technique of essential aroma extraction in which EOs components are solubilized on wax or fat. Fat have the property of absorption and, when fragrant flowers are brought in contact with fat, it absorbs the perfume released by the flowers (Fokou *et al.,* 2020). In this process, the fat is taken on the plates which are made up of glass and is warmed to about 50ºC. The fat surface is covered with the petals and kept as it is for many days until the fat is saturated with the EOs. The petals are removed from the fat and then the digestion of fat takes place with ethanol. The ethanol dissolves the oil present in the fat. Sometimes, the little amount of fat is also dissolved ethanol; it is separated by cooling to about 20ºC. The mixture of alcohol and EOs is distilled under reduced pressure to remove the solvent (Ansari, 2016).

Non-conventional or Modern Extraction Methods

There are many disadvantages of conventional methods of extraction of volatile oils so further modification of extraction techniques has been made. Conventional methods involve high temperature which affects the quality of EOs, and also time taken by process is very large. Many components of volatile oil losses and degraded due to this (Usai, *et al.*, 2011; Hanaa *et al.*, 2012).

The new extraction techniques overcome these disadvantages. Decline the extraction time, energy consumption, solvent used and carbon dioxide discharge are the main features of modern methods (El Asbahani *et al.*, 2019).

Supercritical Fluid Extraction (SFE)

SFE is most extensively used method for extracting EOs. It provides quick extraction at moderate temperatures, no need of clean-up steps and organic solvents. This process requires supercritical fluid. The supercritical fluid state depends upon two parameters i.e. fluid's critical pressure and critical temperature (El Asbahani *et al.*, 2019). Carbon dioxide (CO_2) is an ideal supercritical solvent as it easily reach critical point. It is non-explosive, non-toxic, readily available, easily eliminated from extracted products and obtainable in pure form and at low cost (Guan, 2007; Ghannadi *et al.*, 2012; Shamspur *et al.*, 2012). The principle includes the use and recycle of fluid in repetitive steps of compression and decompression. The supercritical state of CO_2 can be attained by extremely compressing and heating this fluid. The fluid is then permits through the plant material to load volatile matter or extract. Then decompression step takes place where the mixture of CO_2 and plant extracts or oil are separated, the fluid is slowly decompressed to isolate the extracts or oil from the CO_2. The CO_2 is free from second separator and reused into storage

tank, and the final product is free from solvent residue because CO_2 easily becomes gas under normal atmospheric pressure and temperature (Fornari *et al.* 2012).

Subcritical Extraction Liquid

Numerous researchers reported the use of water at its subcritical state and this is a good alternative of extraction of EOs. When the liquid reaches at the pressure more than the critical pressure and lesser than the critical temperature or *vice-versa*, then it is a subcritical stage of a liquid. The fluids such as water and CO_2 can be used to extract EOs in this method. The properties of subcritical state of fluid are low viscosity, low density and improved diffusivity between gas and liquids. The EO isolation is fast in this method which is conducted at a low temperature (Özel *et al.*, 2006). The required duration of extraction is only 15 minutes. Essential oils with higher amount of oxygenated components and with without terpenes can be obtained which have more valuable properties (Tongnuanchan & Benjakul, 2014).

Microwave-Assisted Hydrodistillation (MAHD)

Advancement of hydrodistillation technique is MAHD which uses a microwave oven for the extraction of the plant's active constituents (Golmakani *et al.*, 2008). Extraction techniques which are used conventionally are time and solvent consuming and also unsafe thermally (Mandal *et al.*, 2007). This method have shown reduction in both the time of extraction and the solvent required, it minimize the impact on environment as it emits less CO_2 in the atmosphere (Lucchesi *et al.*, 2004; Ferhat *et al.*, 2006) and consuming very less energy as compared to conventional extraction methods (Farhat *et al.*, 2009). MAHD is used as a heating principle and based upon its direct impact with polar solvents and is controlled by two phenomenon's i.e. ionic conduction and dipole rotation, which occurs simultaneously in maximum cases (Letellier *et al.*, 1999).

Ultrasound-Assisted Extraction (UAE)

UAE facilitates the extraction of components like oils, proteins, polysaccharides, etc. (Vilkhu *et al.*, 2008). The phenomena of cavitation, that is, production and breakdown of microscopic bubbles are effects of ultrasound. Bubbles collapse violently when its size increases. Induction of mechanical forces takes place as a result of this violent collapse leading to damage of membrane of the cell (Cameron *et al.*, 2009), and results in high yield and increased speed of extraction. Ultrasound, no doubt is an expensive in cost but it is an alternative to conventional and latest commercial oil production processes too.

BIOLOGICAL APPLICATIONS OF ESSENTIAL OILS

EOs has been well recognized to possess various different biological activities *in vitro* and *in vivo*. EOs are one of the most important phytoconstituents which exhibit marked biological effects and are well known for their antimicrobial, antiseptic antifungal and as preservative material since the ancient times. Several EOs extracted from plants developing in different environment often affect the compounds of the EOs within the same botanical species. The biological activity of EO depends on various factors such as time of session of harvesting, method of extraction, and their conservation (Bakkali *et al.,* 2008).

Therefore, there is a strong connection is between, chemical compositions of medicinal plants and environmental parameters which directly affect the biological effect of volatile oil. Therapeutic potential of EO can be utilized in management of several disorders. Usually stored in specialized cells or glands and in cavity within specific areas of the plant, such as rhizome, stems, bark, leaves, wood, fruit, and seeds, (Miguel, 2010). Essential oils can go in the body by diverse ways, such as inhaling, via skin absorption and by taking through oral route.

Various EOs produce from plants and useful for several therapeutic property, such as analgesic (peppermint and clove); antifungal (lemongrass); antibiotic (tea tree and lavender oil); anti-inflammatory (lavender and clove); sedative (German chamomile and valerian); antiseptic (lemon grass oil, lavender); antispasmodic (coriander, fennel, dill); aphrodisiac (garlic, black pepper, jasmine, sandalwood); carminative (peppermint, fennel); diuretic (grapefruit and lemon); euphoric (Roman chamomile, jasmine); expectorant (eucalyptus, fennel) laxative (peppermint, black pepper, fennel, orange,); rubefacient (lemongrass, rosemary, peppermint and black pepper) antidiarrheal (cinnamon, basil, ginger, black pepper); vasodilator (black pepper and eucalyptus); bioenhancer (black paper) spasmolytic (carway, coriander); immunomodulatory (holy basil, ginger, sage, clove) psychotropic (Acorus, parsley); and anticancer (sage) (Hajhashemi *et al.*, 2002; Abdollahi *et al.*, 2003; Price & Price, 2007; Carrasco *et al.*, 2009).

The recent advance of using natural compositions in pharmaceutical and food preservation has led to an increasing attention in use of essential oil. The activities of EOs are produced or imparted by single compounds or may be due to synergistic effect of essential oil components. The main function of EO in plant is to defend plant from various predator pathogen and microbes (Bassolé & Juliani, 2012; Lang & Buchbauer, 2012).

Over thousands of years continuously essential oils is use as a medicinal agent due to a wide range of biological, antimicrobial, and other valuable effects. The history of use of essential oil is as ancient as human civilization.

Usually in order to succeed a significant biological, antimicrobial and/or antioxidant effect, a comparatively high concentration of essential oil necessary (Gutierrez *et al.*, 2008). Thus, the essential oil of plants like thyme, clove, garlic, rosemary, cinnamon, or their components, can be used single or in combination with other, to recover the shelf life of pharmaceutical preparation and food products. Essential oils may produce toxic effect at high dose. The toxicity of essential oils can be estimated by animal cells line or *in vivo* animal models. The excess ingestion of essential oil by human has shown common toxic effects like nausea, vomiting, and abdominal cramps whereas dermal exposure may cause rashes, redness, and burning sensation (Prashar *et al.*, 2004; Suschke *et al.*, 2007). So toxicity degree should be first examined when they are employed for purpose of therapeutic, especially in the fields of cosmetics, flavors and food.

ANTIMICROBIAL FUMES

EO fumes are recognized for their antimicrobial potential since the B.C (4th century) though; the potential of these EO fumes is explored too late. Recently, the use of various EO like bergamot oil, lavender oil and eucalyptus oil show wide range of antimicrobial effects against various bacteria and fungus. Fumes of EO work as strong antimicrobials, due to potent antimicrobial agent in field of food science and clinical areas. The main drawback of EOs is that they show their remarkable antimicrobial potential when tested in a microbial culture but in food organizations, so high concentrations are essential to carry

about the same effect. A recent study confirms that antimicrobial vapor phase of EO are more effective as comparison to liquid phases (Inouye *et al.*, 2003). The various constituents of EOs determine their relative volatilities and appearances of their vapor (Burt, 2004). The vapor phase being more effective due to lipophilic molecules in the aqueous phase linked to form micelles and therefore suppress that attachment of the EOs to the organism, whereas the vapor phase allows the molecule attach freely this is the reasons that to use EO as fumes (Inouye *et al.*, 2003). Inhalation of EO in the form of fumes was taken in ancient times. Vapor inhalation in smoke form collected from bay leaves produced visions that came to the oracle at Delphi (Thompson, 2003). In 4th century B.C. (During ancient times) when they were used as antidotes poisoning and breathe in vapor form to easiness the throat. Ancient Egyptians also used EO vapors as perfumery, medicine and spiritual life (Edris, 2007). In *in vitro* screening mainly two methods are used and also assess antimicrobial potential of EOs fumes. Diffusion method is the first method was adapted, where zone of inhibition measured to check antimicrobial potential. In the second method, the EOs fumes and several micro-organisms are sited distinctly into an airtight environment and tested for sensitivity to any one EO fumes at one time. The main demerit of this method is that it not a very cost-effective method due to need of large quantity of EO. However, this method is efficient in the assessing of inhibitory effects of EO fumes on surfaces and in air (Doran *et al.*, 2009; Fisher & Phillips, 2009; Laird *et al.*, 2012). Various home used spices and drugs such as cinnamon, clove, ginger, EO fumes have been already showed promising antimicrobial effect against *Aspergillus flavus* and *Penicillium islandicum* (Lopez *et al.*, 2005). EOs fumes of thyme, nutmeg and sage showed significant antimicrobial effect against *Aspergillus* sp. and *Penicillium* sp. *in vitro* (Tullio *et al.* 2007). Interestingly, *M. piperita* fumes totally inhibit development of a wide variety of fungi and yeasts with *Aspergillus* sp. and *Penicillium* sp. by disc diffusion and time-kill examines. EO of *E. globulus* (Tyagi & Malik, 2011), Lemongrass fumes (Tyagi & Malik 2010) thyme, fennel and lavender (Soylu *et al.*, 2006). The use of EO fumes in food material is very common, and used frequently due to their antimicrobial nature to successfully control food pathogens and food spoilage organisms, such as bacterial and fungal species. One of the main advantages of using EO in vapor phase is that, the components of EO do not distress the organoleptic properties of the food material as EO in liquid form did. Various EO such as, citrus oil, eucalyptus oil thyme oil, oregano oil, cinnamon oil fumes (Paparella *et al.*, 2008) are applied to control microbial contamination in food material. So there are various evidence that EO in vapor phase are effective antimicrobial as when used in liquid form. The main advantage of using EO fume is use of lower concentrations, with more or same antimicrobial activity, and there use in a range of environments, there is not a specific classification that particular EOs fume is effective against particular microorganism. So the spectrum of movement of each EO fumes wants to be recognized by experimentally.

CONCLUSION

Essential oils are naturally occurring compounds also known as volatile oil. In conventional method, hydrodistillation is the most suitable, easy to carry out procedure for isolation of volatile oil from all parts of the plants as comparison to other methods but now day's modern techniques are available for extraction of volatile oils due to many disadvantages of conventional method. Conventional methods involves high temperature which affects the quality of EOs, and also time taken by process is very large. Many components of volatile oil losses and degraded due to this. Essential oils possess various medicinal and pharmacological activities due to its important constituents and also used in the perfume and cosmetic

industries. EO can be used as antimicrobial, antiseptic, antifungal, anticancer and wound healing. EO fumes are recognized for their antimicrobial potential since B.C. Fumes of EO work as strong antimicrobials, due to potent antimicrobial agent in field of food science and clinical areas. EOs fumes of thyme, nutmeg and sage showed significant antimicrobial effect against *Aspergillus* sp. and *Penicillium* sp. The essential oils market rapidly growing day by day in the whole world due to its good results.

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Section 3

Advanced Biological Technologies in Herbal Drug Discovery

Chapter 21
Implications and Future Perspectives of Nanomedicine and Plant-Based Biogenic Nanoparticles (NPs) for Cancer Management

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ABSTRACT

In the modern era of science, nanotechnology has the ability to circumvent numerous disadvantages of conservative healing preparations. Important progress has been made towards the use of tailored nanomaterials (NMs) to treat the cancer with efficiency, specificity, and high sensitivity. Tailored NMs are operationalized with precise ligands that can predictably target the cancer cells and deliver encapsulated payloads meritoriously. Moreover, NMs can also be deliberated to increase the drug loading, controlled release, improved half-life, and selective distribution by altering their size, surface chemistry, composition, and morphology. The conservative cancer treatments have provoked the event and applications of nanomaterials. The emerging evidence suggests that nanomedicines will provide the next-generation stages for anticancer remedies.

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INTRODUCTION

Cancer is one of the leading causes of mortality in the globe with year 2020 recorded an estimated 10 million deaths. Moreover, the World Health Organization (WHO) warned tremendous increase in the cases by three folds in next two decades (Andleeb *et al.,* 2021). Notwithstanding energies to alleviate risk factors in latest decades; the occurrence of the cancer rises continuously (You & Henneberg, 2018). Present principles of care combine precise performance of cancer with the radiation therapy and chemotherapy which known for significant adverse effects (Naidu *et al.,*2004), with most approaches directing non-specifically any speedily dividing cells regardless of whether they are cancerous or not. Therefore, it is domineering to improve the effective preparations that can address the contests and deliver choosy targeting of the tumor sites devoid of substantial loss to the viability of the vigorous tissues (Navya *et al.,* 2019). In the model of medicine, nanomaterial-based medicine gaining popularity as for delivering drugs, and development of nano-based implants, and to establish a novel *in-vitro* diagnostics (Shi *et al.,*2010).

Breast cancer (13.7%) is the most often reported cancer worldwide, followed by colorectal cancer (11%). Because these patients' immune systems are severely impaired, present chemotherapies for these two main tumours frequently result in secondary problems such as infections by bacteria, fungus, and viruses. For the treatment of breast cancer, a variety of cytotoxic medications are utilised, including doxorubicin, cisplatin, and bleomycin; nevertheless, they all have downsides and are ineffective. Nanomedicine is concerned with the development of innovative therapeutic and diagnostic modalities for human use using precision-engineered nanoparticles. Nanotechnology and medicine have merged to create new therapeutic and pharmacological possibilities. Nanoparticles could be used to target and treat cancerous cells as anticancer nanomedicines. The NPs could be used as antiangiogenic, anticancer, antipermeability, and antiproliferative molecular probes. AgNPs have been claimed to have the highest degree of commercialization among nanoparticles, and have gained a reputation in sectors such as medicine and materials research. AgNPs have unique features that enable these nanomedicines to successfully manage a variety of pathological diseases. AgNPs are effective against hepatitis B, respiratory syncytial illness, herpes simplex infection type 1 and monkey pox infection due to their antiviral characteristics (Khan *et al*., 2021).

An extensive field of NMs has been prepared that could be exploited for development of anticancer medicines by manipulating the morphological and chemical features to control the functions of organic, biological, inorganic, and protein (range of 1–100 nm) based nanoparticles. The Nanocrystals, polymeric micelles, albumin and chitosan based nanoparticles and liposomal formulation, help to overpower such tasks. The use of nanomaterial and nanomaterial-based therapeutic agents hints to reduce the risk to the patients and upgraded their survival (Jabir *et al.,* 2012).

Many metallic NPs have been designed for treatment of cancer, with copper (Cu), gold (Au), silver (Ag), and zinc (Zn), being the most common. The creation of ROS in cellular compartments is credited with these NPs' anticancer potential, which is responsible for activation of the necrotic, apoptotic, and autophagic death pathways (Andleeb *et al.,* 2021). The pharmacokinetics of nano therapeutics has been discovered in preclinical and clinical trials across species. Only a few researchers have compared data from different animal models for the determination of the safety and effectiveness of the nanoparticles in humans (Gerlowski & Jain, 1986).

Nanoparticles are classified based on their dimensions. Materials with zero dimensions are larger than 100 nm measured on the nanoscale. Thin films or manufactured surfaces or coatings are one-dimensional

NMs. Nanotubes, nanofibers, nanowires, and nanopolymers are two-dimensional nanoparticles. The quantum dots, fullerenes, and dendrimersare three-dimensional nanoparticles (Haque *et al.,* 2010).

EFFECT OF PHYSICOCHEMICAL PROPERTIES

The level of tumor addition and *in vivo* distribution of NMs is determined by their form and size (Sun *et al.,* 2014). Three distinct sizes and two different shapes of siRNA-conjugated gold nano structures (13 nm sphere, 50 nm sphere, and 40 nm) has been designed to test the in vitro response of U87 glioma cells affecting the expression of isocitratedehydrogenase-1 (Yue*et al.,*2017). The surface charge of NMs directs their applicability and biological effectiveness (Navya & Daima, 2016). Usually, positively charged NMs may assume proficiently at membranes of the cells due to presence of opposite charge on the cell surface (Zhao *et al.,* 2011).

To prepare NMs for the specific biomedical claims, surface chemistry strategy is crucial. Engineered non materials reduce toxicity and boost stability in addition to modifying the surface corona (Navya & Daima, 2016).

NANOMATERIAL AS DRUG DELIVERY AGENTS

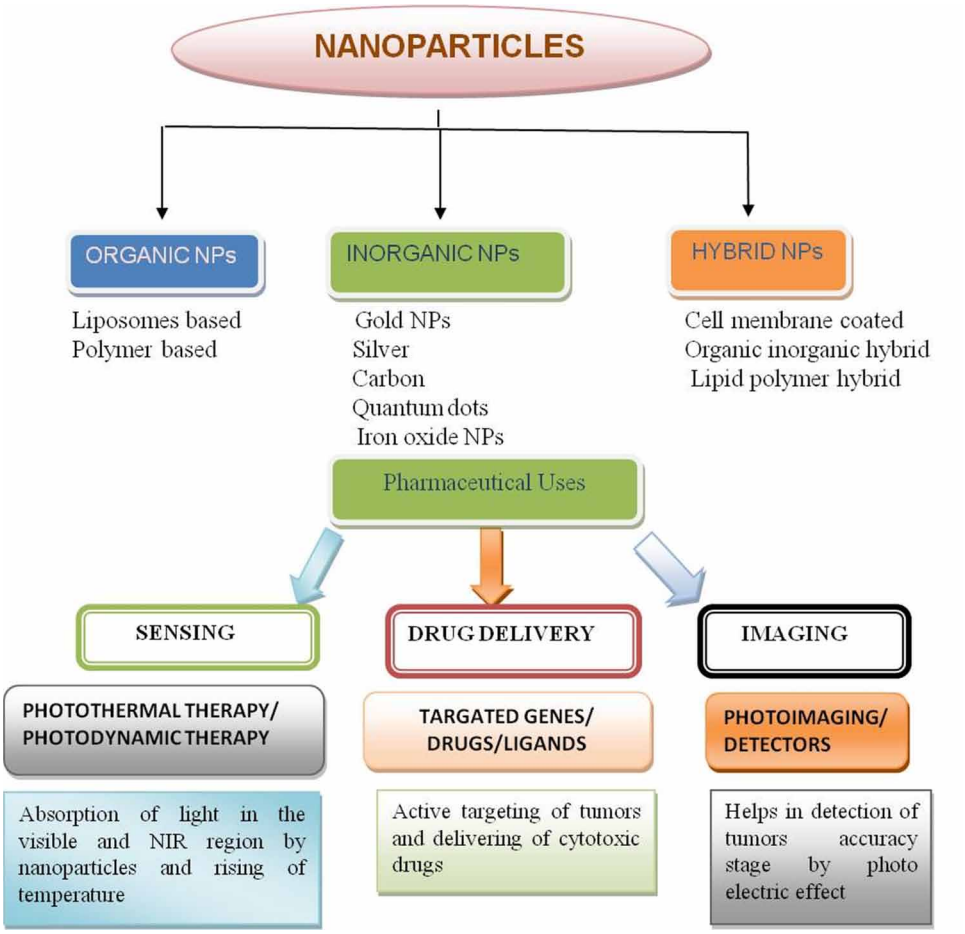
35.3.1 Inorganic NPs

Amongst the inorganic NMs, metal NPs and metal oxides have expanded notable deliberation because of their extraordinary possessions and current development in the central consideration through the progress of pioneering methods. Inorganic nanoparticles with precise characteristics have recently been produced and used in biological applications, particularly in cancer treatment and management. Metal nanoparticles and metal oxides have risen to prominence among inorganic nanomaterials due to their unique features and recent advances in fundamental understanding through the development of novel methodologies. Mesoporous silica nanoparticles and carbon-based nanostructures are two other prominent nanomaterials that play an important role in medication delivery. Table 35.1 shows a variety of inorganic nanocarriers that can be used to deliver anticancer treatments (Gautam *et al.,* 2021).

Metal Nanoparticle and Metal-oxides

Because of their controlled form and size, biocompatibility, and smooth surface functioning, metal and metal oxides NPs have gained popularity as the vehicles for drug delivery. The tunable size and shape, biocompatibility, and ease of surface functionalization, of metal and metal oxide nanoparticles make them most valuable materials for drug delivery. Noble metal nanostructures, especially Au nanoparticles, are commonly employed for medication delivery. Wan et al. (2018) investigated the anticancer properties of docetaxel conjugated Au doped apatite in vitro. The substance was found to have enhanced bioavailability at the location, as well as higher cytotoxicity against human liver cancer cells HepG2. Furthermore, a fluorescent photodynamic therapy (PDT) drug has been developed comprising of Pc4 coated Au nanoparticles that increase the process of receptor-mediated endocytosis due to the presence of prostate-specific membrane antigen (PSMA-1) ligand that helps in targeting of the disease biomarkers

Figure 1. Classification of organic, inorganic and hybrid nanoparticles and their application in treatment and detection of cancer.



resulting in the increased tumour residence time. *In vitro* and *in vivo* studies have been used to assess the efficacy of a theranostics for prostate cancer (Navyav *et al.,* 2019; Gautam *et al.,* 2021).

Gold Nanoparticles (AuNPs)

The decent metal nanostructures, predominantly AuNPs, are extensively applied for conveying drugs. Au nanoparticles coated with two different anticancer medications have been shown to not only extend drug circulation time but also improve drug targeting and lower the chance of drug resistance (Safwat *et al.,* 2018).

Silver Nanoparticles (AgNPs)

AgNPs have also been shown to be anticancer agents that can be used to treat a variety of cancers (Kumar *et al.,* 2016). Silver (Ag) nanoparticles, like Au nanoparticles, have been shown to be effective anticancer

agents in the treatment of a variety of cancers. Ag nanoparticles have been employed to deliver medications with the potential to improve therapeutic parameters. For cancer therapy, Ag nanoparticles coupled with phytopharmaceuticals can be used as non-toxic delivery vehicles, contrast agents, and photothermal agents. Prostate and colon cancer can be treated using biogenic Ag nanoparticles. Ag nanoparticles made from *Indigo ferahirsuta* leaf extract and pollen extract of *Phoenix dactylifera*, for example, demonstrated dose-dependent cytotoxicity against various malignancies. A novel drug delivery method was created using Ag nanoparticles coated with a camptothecin-based polymer pro drug for long-term drug release based on pH sensitivity. Co-delivering medications with particles with varied physicochemical properties has been proposed as another promising technique for suppressing tumor metastasis and overcoming treatment resistance (Navya *et al.,* 2019; Gautam *et al.,* 2021).

Iron Oxide Nanoparticles (IONPs)

The Iron oxide nanoparticles (IONPs) aroused as the agnostic NPs given a means to image the response of the tumors, toward the drugs delivered during the clinical trials for cancer (Manatunga *et al.,* 2018). Iron oxide nanoparticles (IONPs) have developed as therapeutic nanoparticles that can be used to image drug distribution and tumor response, addressing unmet clinical problems in cancer treatment. Prostate cancer is currently being treated with paclitaxel drug loaded on double receptor targeted iron oxide nanoparticles. These iron oxide nanoparticles were successfully ingested by the human prostate cancer cell line PC-3, according to the findings. When compared to normal prostate epithelial cells, in vitro magnetic resonance imaging verified the increased binding and accumulation of ironoxide nanoparticles in PC-3 cells. Using iron oxide nanoparticles, a theranostic nanoparticle was recently developed to improve intra-tumoral drug delivery by overcoming drug resistance and delivering image-guided drug delivery while minimizing systemic toxicity. The uptake and dispersion of iron oxide nanoparticles in the PANC02 mouse pancreatic cancer cell line were studied using three different targeted nanoparticles and one non-targeted nanoparticle. The study also showed that remaining tumors could be detected after intraperitoneal medication, implying that drug-resistant tumors might be removed using image-guided surgery (Navya *et al*., 2019).

Carbon-based Nanomaterials

Due to its attractive qualities like to cargo high amount of drugs, large surface area, and ease to adjust surface, carbon-based nanomaterials have been widely researched in cancer imaging and diagnosis, as well as for delivery system. Carbon nanotubes (CNTs) and graphene are the well-studied carbon nanomaterials in therapeutic applications related with the cancer. Carbon nano tubes are used as efficient system for the delivery of drugs to target cancer cells more effectively. Recent research on multi-walled carbon nanotubes (MWCNTs) for drug co-delivery has indicated that drug release at the cancer site, as well as cell uptake, has the potential to cure multi-drug resistant cancer. MWCNTs have been synthesized that have high drug loading ratio along with active targeting ability and better circulation half-life (Wang *et al.,* 2017). A potential multimodal nanomedicine for cancer treatment has been developed by utilizing the heat generated by the pH-sensitive nano-platform in response to the light absorption when exposed to near-IR (NIR) light along with the toxicity of DOX. In another study, TiO2–Au nanocomposite was used to decorate multi-walled carbon nanotubes, and the system was found to be effective in generating toxicity in A549 and MCF7 cancer cell lines (Navya *et al*., 2019).

Mesoporous Silica Nanomaterials (MSNs)

The MSNs are among the hopeful nanocarriers for well-organized delivery of the cancer therapeutics. The opportunity of using MSNs as probable nanocarriers has determined attention in many biomedical claims (Manzano & Vallet-Regí, 2018). Because of the ease with which mesoporous silica nanoparticles can be modified to have varied properties, multifunctional delivery platforms can be designed. Many researchers have used mesoporous silica nanomaterials to load cargos and convey them to tumor tissues because of these characteristics. Because of the medication's solubility, stability, and bioavailability, many anticancer therapeutic applications are limited. Li *et al*. (2018) created unique nanocarrier systems for releasing the curcumin precisely at the targeted tumor site environment. Curcumin was delivered to breast cancer cell lines loaded with hyaluronan or polyethyleneimine-folic acid using these surface changeable mesoporous silica nanomaterials, which were tested in a mouse xenograft model (Navya *et al*., 2019).

Organic Nanomaterials (ONMs)

The ONMs are hopeful applicants for the progress of drug delivery systems. The low toxicity, have allowed the nano-medicine investigation community to practice ONMs for releasing the drugs in a controlled manner and at very precise tissue location (Daima *et al.,* 2018).

Liposomes

Liposomes are closed spherical shaped structure made up of natural or synthetic phospholipid bilayer adjoining an inner aqueous phase. Consistently, these vehicles compromise numerous other compensations, with self-assembly, biocompatibility, and high drug cargo loading. Liposomes are good drug-carrier systems because of their physical similarities to biological membranes and their capacity to integrate with a variety of compounds. In biomedical uses of liposomes, significant progress has been achieved in enhancing the therapeutic index of encapsulated medicines over the last 20 years. Different types of liposomes are employed as drug delivery platforms to improve the efficacy of cancer treatments. Liposomes can be attached on the exterior surface with poly(ethylene glycol) (PEG), targeting ligands and/or antibodies, and polysaccharides to improve solubility, increase hydrophilicity, and provide passive and active targeting functionalities, resulting in high therapeutic efficacy and minimal toxicity (Sercombe *et al.,* 2015; Bozzuto & Molinari, 2015).

Polymeric NPs

Beneficial molecules will be enclosed, adsorbed, or conjugated in the polymer matrix of the polymeric nanoparticles, which are colloidal NPs. Artificial and biological polymers can be utilized to make these NPs, and they've been widely used in drug-delivery systems. Because of their specific features, such as drug solubility, stability, and preferential accumulation, these nanoparticles can be modified for a variety of biological applications. The diverse chemical composition, charge, and physical structure, polymeric nanoparticles serve as a varied substrate for drug delivery. Furthermore, due of their customizable drug release kinetics, they have gained commercial importance. The cancerous cells have been targeted and polymeric nanoparticles have been used for transfer of drugs efficiently. The tumor-specific targets have been explored on the cell surface for destroying the tumor cells. To target specific cells, different ligands

such as aptamers, peptides, proteins, antibodies, and tiny compounds have been utilized. Targeting cells using nanoparticles resulted in extremely precise cargo delivery, resulting in high therapeutic concentrations within the cell. Several studies have been conducted. Several studies have shown that targeting moieties improve anticancer activity. The drug docetaxel (DTX) has been successfully delivered using the drug delivery system comprising of surface modified polylactic acid (PLA) nanoparticles for treating the liver cancer (Masood, 2016; Navya *et al.,* 2019).

Table 1. Classification and Functions of Nanoparticles

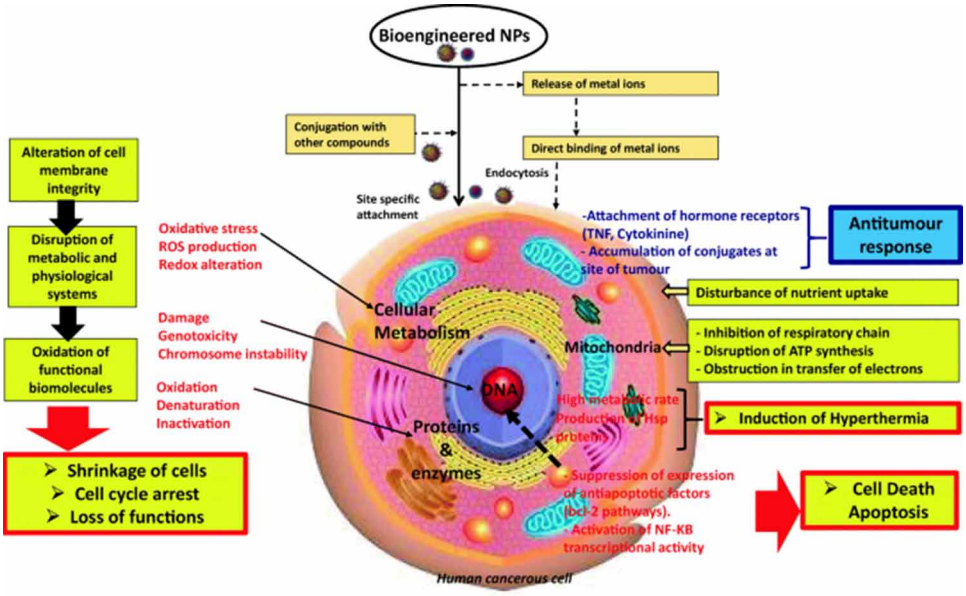
Nanocarriers	Materials	Drug	Target	References
Metal NPs	Apatite stacked Gold NPs	Docetaxel	Human liver cancer (*in vitro*)	Wan *et al.,* (2018)
	CTAB and gold nanoparticles	Fluorouracil	Human skin cancer (*in vitro/ in vivo*)	Safwat *et al.,* (2018)
	AgNPs	Imatinib	Human breast adenocarcinoma (*in vitro*)	Shandiz *et al.,*(2017)
	PEG and AgNPs	Methotrexate	Human breast cancer	Muhammad *et al.,*(2016)
Carbon NPs	PEG and single walled carbon nanotubes	Cisplatin	Head and neck cancer (*in vitro/ in vivo*)	Bhirde *et al.,*(2010)
	Human serum albumin, single walled carbon nanotubes	Paclitaxel	Human breast cancer (*in vitro*)	Shao *et al.,*(2015)
Mesoporous silica NPs	PEG amino-beta-cyclodextrin, folic acid, mesoporous silica nanoparticles	Doxorubicin	Breast cancer (*in vivo*)	Zhnag *et al.,*(2013)
	Aptamer, mesoporous nanoparticles	Doxorubicin	Colon cancer (*in vitro*)	Xie *et al.,*(2016)
Liposomes	DPPC, MPPC	Tamoxifen, imatinib	Human breast cancer (*in vitro*)	Jose *et al.,*(2018)
	DSPE-PEG2000-Pen, DSPE-PEG2000-Tf	5-Fluorouracil	Human glioblastoma (*in vitro*)	Lakkadwala and Singh,(2018)
Polymeric NPs	PLA	Calcitriol	Human breast cancer (*in vitro*)	Nicolas *et al.,*(2018)
	PLGA, PEG, Chitosan	Curcumin	Human pancreatic cancer (*in vitro*)	Arya *et al.,*(2018)

BIOLOGICAL SOURCES OF NANOPARTICLES SYNTHESIS

Fungal-based Nanoparticles

An efficient and environmentally acceptable method for the production of (AgNPs) utilizing aqueous culture filtrate of *Pestalotiopsis microspora* has been disclosed in a study. The presence of a characteristic absorption peak at 435 nm in ultraviolet visible examination validated the synthesis of AgNPs. In the fungal filtrate, FT-IR spectroscopy revealed the presence of phenolic chemicals and proteins, which are likely involved in the production and capping of AgNPs. The AgNPs were spherical in shape and 2–10

Figure 2. Mechanism of Interaction of Bioengineered Nanoparticles and Cancerous cells (Karmous et al., 2020).

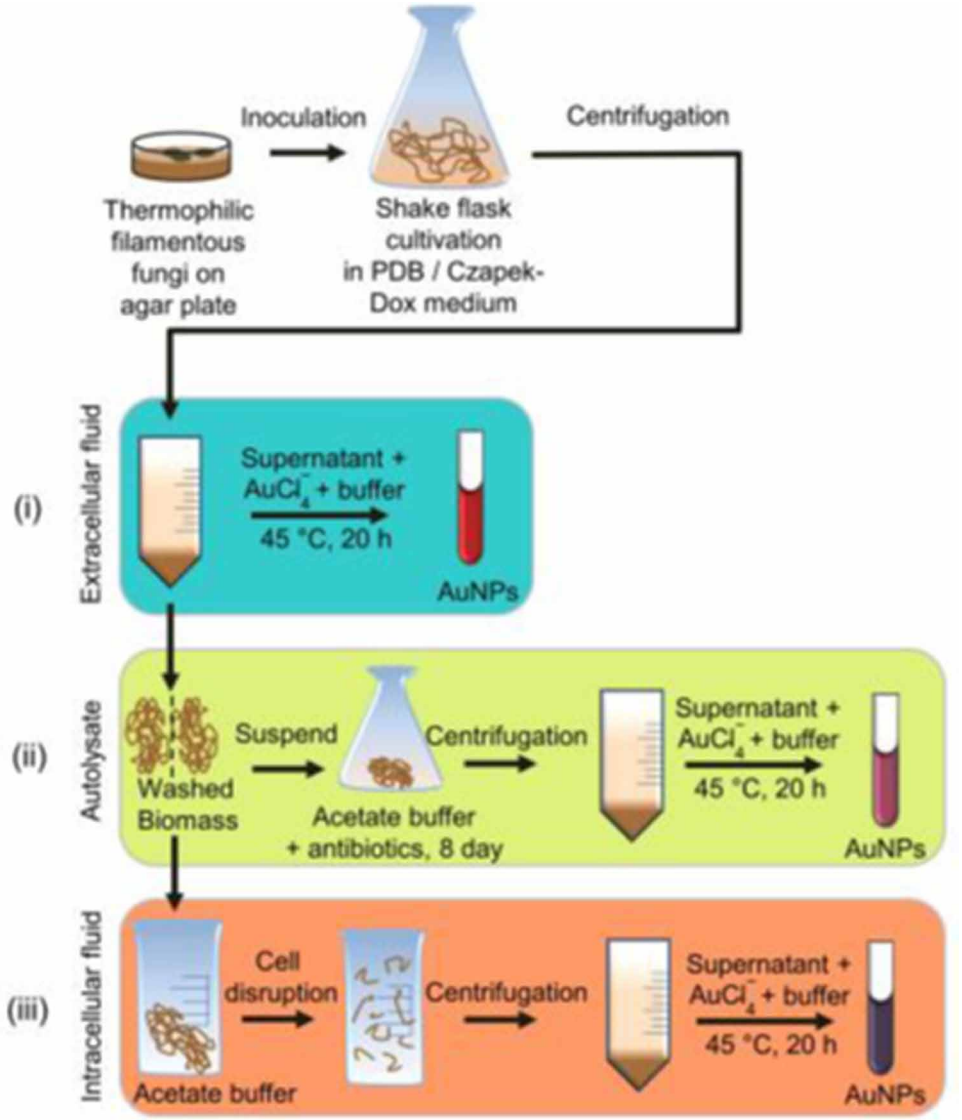


nm in size, according to the TEM. The crystalline nature of AgNPs with a face-centered cubic (FCC) lattice phase was determined using selected area electron diffraction and X-ray diffraction experiments. The biosynthesized AgNPs had a high negative zeta potential of -35.7 mV, according to dynamic light scattering studies. Strong cytotoxic effects have been reported against PC3 (human prostate carcinoma, A549 (human lung adenocarcinoma, SKOV3 (human ovarian carcinoma, and B16F10 (mouse melanoma) cells lings with the IC_{50} values of 27.71, 39.83, 16.24 and 26.43 µg/mL, respectively. Normal cells (Chinese hamster ovary cell line, IC50 =438 µg/mL) were found to be biocompatible with the biosynthesized AgNPs. On most vulnerable SKOV3 cells, cytological observations revealed concentration-dependent apoptotic alterations such as cell shrinkage, cell membrane blebbing, pyknotic nuclei, and karyorrhexis followed by destructive nuclei fragmentation (Netala *et al.,* 2016; Gautam *et al.,* 2021).

Algal-based Nanoparticles

The shape of the NPs is kinetically regulated growth process in a solution where certain form is adopted by the faces with low energy. Further the presence of the surfactant or templating agent results in development of the crystal by lowering the interfacial energy (Xia *et al.,* 2003). Commercially many surfactants are used as capping agents as well as templates for the NPs synthesis with a variety of morphologies up to this point. However, the major concern is the complete elimination and biodegradation of these compounds. At the present time, Green synthesis process for the nanoparticles synthesis is trending due to its environmentally friendly and bioinspired methods. NPs of greater quality can be created by understanding the capacity of naturally existing biomolecules to change the shape or size of a crystal. The employment of several species of algae in the synthesis of metallic NPs has prompted scientists to

Figure 3. Production of various extracts from fungi and production of AuNPs by various methods using: (i) extracellular extract; (ii) auto lysate; (iii) intracellular extract (Molnar et al., 2018; Gautam et al., 2021).



develop "nature-friendly" methods. Because of their potent antibacterial properties, Ag NPs have gotten a lot of interest.

As a result, synthesis takes place in the presence of microalgae, with the metabolites released by the algal culture causing silver ions to be reduced. The optical characteristics of the NPs can be changed depending on the particle size (Merin *et al*., 2010). Silver nitrate was shown to be reduced in the presence of the seaweed *Chaetomorpha linum*. The extract's metabolites (flavonoids and terpenoids) were shown to be excellent capping and stabilising agents, resulting in the creation of NPs with an average size of 30 nm that might be used in medicine (Kannan *et al*., 2013). Biomolecules found in algae species,

such as polysaccharides, are also crucial in influencing the size and shape of Ag NPs. The marine algae *Pterocladia capillacae, Jania rubins, Ulva faciata,* and *Colpmenia sinusa* are effective in supporting the production of polydispersed and spherical Ag NPs capable of immobilising on cotton fibres. As a result, they function as antibacterial agents (El-Rafie *et al*., 2013). Using microalgae as a bio-template, a composite of nano Ag-$CaCO_3$ was created in an efficient and environmentally friendly manner. Carbon dioxide (CO_2) was mineralized using a microalga (*Chlorella* sp.) to generate calcium carbonate ($CaCO_3$) microspheres (Sahoo *et al.,* 2014).

The generation of $CaCO_3$ particles was discovered to be caused by the surface charge of microalgae cells. The positively charged Ca^{2+} ions agglomerated on the surface of negatively charged algal cells due to electrostatic interactions, and so served as a driving force for the nucleation process. The size of microspheres was also affected by the concentration of Ca^{2+} ions. The larger the size of the $CaCO_3$ microspheres, the higher the concentration, maintaining the concentration of algal cells constant and favouring heterogeneous nucleation. The microspheres were employed as an inexpensive matrix for the production of Ag NPs. The composite demonstrated an effective antibacterial action against model bacteria such as *E. coli, Psychrobacter alimenterius,* and *Staphylococcus euroum*, paving the door for its commercialization as paint additives (Sharma *et al*., 2019).

Plant-based Nanoparticles

In the current study, we used *Heliotropium bacciferum* extract and AgNO3 as starting ingredients to make silver nanoparticles (AgNPs). Various spectroscopic and microscopic techniques were used to confirm the size, shape, and structure of produced AgNPs. The average size of biosynthesized AgNPs was discovered to be between 15 and 20 nanometers. In breast (MCF-7) and colorectal (HCT-116) cancer models, the anticancer potential of these AgNPs was assessed using a battery of tests including (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (MTT), scratch, and comet assays. The expression pattern of apoptotic (p53, Bax, caspase-3) and antiapoptotic (BCl-2) genes by RT-PCR validated the toxicity of AgNPs towards cancer cells. AgNPs had IC50 values of 5.44 and 9.54 µg/mL in MCF-7 and HCT-116 cell lines, respectively, in the cell viability assay.

ANTICANCER ACTIVITIES OF BIOGENIC NANOPARTICLES

Silver NPs (AgNPs)

The biological AgNPs can be hired against colon and prostate cancer. For example, the AgNPs manufactured by using leaves extract of *Indigo ferahirsuta* L. (Fabaceae) and pollen extract of *Phoenix dactylifera* L. (Aracaceae)have shown anticancer activity against diverse cell lines in a dose dependent manner (Netala *et al.,*2018; Banu *et al.,*2018). *Sargassum vulgare* (Phaeophyceae)-based AgNPs showed the substantial anticancer activity against the human myeloblastic leukemic cells (HL60) and HeLa cells (Lewis Oscar *et al.,* 2016). At various doses of AgNPs (3 to 50 µg/mL), *S. muticum*-based AgNPs showed *in vitro* cytotoxic characteristics against the MCF7 breast cancer cell line for approximately 48 hours, with the highest viability rate of 100.36% reported at 12.5 µg/mL concentration. These AgNPs mainly responsible for generation of ROS intracellularly, which further leads to apoptosis and ultimately death of cancerous cells (Supraja *et al.,* 2016). *S. myriocystum*-based AgNPs has been assessed for their

cytotoxic capabilities against the HeLa cell line at different concentrations (0, 2, 4, 8, 16, 32, 64, 128, 256, to 512 µg/mL) using MTT assay and observed that the AgNP-treated HeLa cell line showed 50% inhibitory (Balaraman *et al.,* 2020). Similarly, different concentration of the silver nanoparticles synthesised using algae showed *in vitro* cytotoxicity propensity against the malignancy MCF-7 cell line when used for24-48 h, with 20 µg/mL MIC value, indicating nuclear fragmentation, cell death, and apoptosis, indicating AgNPs' anticancer potential (Gopu *et al.,* 2020).

Gold NPs (AuNPs)

It has been studied that gold NPs synthesized by use of aqueous leaves extract of *Argemone mexicana* L. showed cytotoxicity in response to the breast cancer cell line (MCF-7). The activation of caspases begins the apoptotic cell death processes (Varun & Sellappa, 2014). The aqueous extract of *Corallina officinalis* L. (Corallinaceae) produced NPs, which indicated the cytotoxicity against human breast cancer cells through necrosis and DNA damage (El-Kassas & El-Sheekh, 2014). The aqueous pollen extract of *P. dactylifera* was used for AuNPs production, which showed the cytotoxicity against breast cancer cells and by modulating the expression of pro (Bcl-2) and anti-apoptotic proteins (Banu *et al.,* 2018). *Acanthophora spicifera*-based AuNPs exhibited robust anticancer potential against the colorectal adenocarcinoma HT-29 cell line at various concentrations (1.88, 3.75, 7.5, 15, and 30 µg/mL) using MTT assay. The MIC value of 21.86 µg/mL was reported, which is responsible for apoptosis, and shrinkage of cells in cancer cell lines (Babu et al., 2020). After incubation with these nanoparticles, *Chaetomorpha linum*-based AuNPs showed in vitro anticancer potential towards the HCT-116 colon cancer cell line in a dose-dependent manner. A series of apoptotic inductions has been identified, including the activation of apoptotic caspase 3 and 9, as well as a decrease in anti-apoptotic proteins such as Bcl-xl and Bcl-2, proving that the AuNPs generated by algae are effective anticancer agents (Acharya *et al.,* 2020).

Copper/copper oxide NPs

Phaseolus vulgaris L. (Fabaceae) based copper oxide NPs has been showed cytotoxicity activity against the cervical cancer. The apoptotic pathways activation was mediated by intracellular reactive oxygen species and used for the detection of growth inhibition and death of cells as assessed by using colony-forming assay (Nagajyothi *et al.,* 2017). The copper NPs have also attracted interest as the carcinogenic nano-entities for their effortless availability, lower price, and metals' close like nessin properties (Manke *et al.,* 2013).These nanoparticles have excellent property of transforming near infrared laser light to heat efficiently for its use in cancer imaging(Zhou *et al.,* 2016).Multiple malignant cell lines have been found to be cytotoxic by a variety of naturally produced Cu/CuO NPs. Plant-based CuO NPs with a diameter of (26.6 nm) were found to have inhibitory effects on cervical cancer cell lines HeLa by starting reactive oxygen species (ROS) mediated apoptosis (Nagajyothi *et al.,* 2017). CuO NPs (12 nm size), synthesised using a green approach exhibited anticancer activity against different cancer cell line like breast cancer (MCF-7), cervical cancer (HeLa) and lung cancer (A549) with a broader range of IC50 values (Rehana *et al.,* 2017). Biosynthesized spherically shaped CuO NPs of 26–30 nm diameters (with a 56.16 µg/mL IC50 value) were used to inhibit MCF-7 breast cancer cell lines (Nisar*et al.,* 2019). The biologically produced CuONPs showed anticancer activity by fragmenting the nucleus to bring apoptosis of lung cancer cell lines A549 (IC50 value of 200 µg/mL) (Sankar *et al.,* 2014).Different sized spherical CuO NPs showed anticancer activity against the breast cancer cell line (AMJ-13),cervical cancer cell lines

(HeLa), lung cancer cell line(A549), ovarian cancer cell line (SKOV-3) and prostate cancer cell lines (PC-3) with very low IC50 values (Harne *et al.,* 2012; Prasad *et al.,* 2016; Sulaiman *et al.,* 2018).

Zinc and Zinc Oxide NPs (Zn/ZnO-NPs)

The biologically synthesized zinc and zinc oxide NPs has gained attention for eco-friendly nanoparticles synthesis due to the metabolites such as alkaloids, flavonoids and phenolics present (Thema *et al.,* 2015). ZnONP has been biologically synthesized using numerous plant portions and their anticancer effect has been studied *in vitro* by using different malignant cell lines. Different shaped biologically synthesised ZnNPs exhibited cytotoxicity against lung cancer cell lines, A549 and Calu-6. The IC_{50} values and size of the nanoparticles vary greatly and affected by the plant source used for their synthesis (Firdhouse *et al.,* 2013). Different plant extracts were utilized for the synthesis of spherical and hexagonal ZnNPs (ranging between 22.5–50 nm), that inhibited the WEHI-3 leukaemia cancer cell lines with varied IC50 values (Min, 2007; Park *et al.,* 2011). The IC_{50} value of biologically produced spherical ZnNPs varied proportionally with the dose applied and was greatly affected by the plant extract used for synthesis (Zhu *et al.,* 2012; Saud Alarifi *et al.,* 2013). The biologically synthesized ZnNPs (sizes 10 ± 1.5 nm) showed inhibitory actions against the CaOV-3 ovarian cancer cell lines (IC_{50} value of 10.8 ± 0.3 µg/mL) (Talalay *et al.,* 2003). The inhibition by biologically synthesized spherical ZnNPs (47 nm size) was observed against colon cancer cell lines HT-29 with (9.5 µg/mL IC_{50} value) (Yang & Xie, 2006). The epidermoid cancer cell lines A43 and A44 and liver cancer cell lines Hep-G2 were shown to have putative inhibitory effects by biologically produced ZnO-NPs (Premanathan *et al.,* 2011; Zhao *et al.,* 2013).

CONCLUSION

Several important progresses have been prepared towards the use of tailored nanomaterials (NMs) to treat the cancer with efficiency, specificity, and high sensitivity. Tailored NMs operationalized with precise ligands that can predictably target the cancer cells and deliver encapsulated payloads meritoriously. Moreover, NMs can also be deliberated to increase the drug loading, controlled release, improved half-life, and selective distribution by altering their size, surface chemistry, composition, and morphology. The conservatively existed cancer treatments have existing natural boundaries that provoked the event and applications of nanomaterial, which compromised a hopeful and harmless dealing. The emerging evidence suggests that nanomedicines will provide the next-generation stages for anticancer remedy. Therefore, in this chapter, a series of biological NMs that are presently being working for the anticancer healings and converse the central role of their biological possessions in the cancer remedy.

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Chapter 22
Nano Particle-Based Targeted Drug Delivery for Effective Treatment of Cancer Disease: Current Updates and Future Prospective

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ABSTRACT

Nanoparticles are currently being used rapidly and tested to overcome some of the limitations of standard drug delivery systems and can be used as an alternative treatment for cancer. These are the most important components of nanomedicine, and they have received much attention as promising programs for drug delivery and cancer treatment. Nanoparticles' ability to synthesize efficiently or by acting on demanded tissues or cells is the basis for implanted plant delivery systems. The primary goal of using nanoparticle-based technology was to improve drug solubility, bioavailability, absorption, and controlled release. In contrast to the last 50 years, nanoparticle-based drug discovery involves a high degree of uncertainty, and the production of pharmacologically active molecules from natural sources is not an alternative.

INTRODUCTION

Nanoparticles are currently being used rapidly and tested to overcome some of the limitations of standard drug delivery systems and can be used as an alternative treatment for cancer treatment. These are the most important component of nanomedicine, and they have received much attention as potential programs for delivery of drug and cancer treatment. Nanoparticles' ability to synthesize efficiently or by acting on demanded tissues or cells is the basis for implanted plant delivery systems. The primary goal of using nanoparticle-based technology was to improve drug solubility, bioavailability, absorption, and controlled release. In contrast to the last 50 years, nanoparticle-based drug discovery involves a

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high degree of uncertainty, and the production of compounds with pharmacological activity from natural sources is not an option. The suitability of several nanoparticles for simultaneous in vivo imaging and cancer treatment has been investigated by many scientists.

Nanoparticles can also be programmed for recognition of the tumorous and cancerous cells and giving accurate and selective drug delivery avoiding interference with the healthy and normal cells. Nanoparticle buildup in malignant cells, in vivo studies and assessment of therapy outcomes, killing cancer cells with minimal adverse effects while safeguarding normally cells are all possible paths for the area of nanotechnology. Nanoparticles can be designed through few changes such as changing their shape, size, physical and chemical properties to program them for targeting the selective cells. They can also target the neoplastic cells either through passive or active targeting. The ability of nanoparticles to actively or passively aggregate in the intended cells or tissues is the foundation of targeting medication delivery systems. Using active or passive targeting techniques, nanoparticles can raise the intracellular concentration of medicines in cancer cells while avoiding harm in normal healthy cells. Drug delivery system (method) include submicron-sized particles (100-1,000 nm), devices or systems made of nano-materials, lipid (liposomes), virus (viral nanoparticle) polymer (e.g., vesicle, micelles, dendrimers or polymeric nanoparticles) and even inorganics.

Targeted drug delivery system, on the bases of nanotechnology, has the capability to conquer several barriers to efficiently targeting a number of different types of cells. They also suggest the possibility of overcoming the main problem of resistance of drug in specific cell and facilitating drug molecule movement throughout obstacles. In comparison with traditional drug delivery system, the nanoparticle-based drug delivery system shows improved efficacy by improving the solubility of hydrophobic drugs, increasing half-life of vulnerable drugs and proteins and allowing targeted and regulated administration of drugs in affected site.

Recent research has focused on nanoparticle surface alterations in terms of improving nanoparticle retention time. Recent advances in nanotechnology have led to the development and improvement of nanoparticle formulations for diagnostic and therapeutic applications. The efficacy of few products i.e., Curcumin, Berberine, Quercetin, Resveratrol, Ellagic acid and has considerably enhanced by the usage of nanocarriers preparation with gold, cadmimum sulphide, silver and polymeric nanoparticles of TiO_2 together with solid lipid nano-particles, crystal nanoparticles, liposomes, superparamagnetic Fe_2O_3 (Superparamagnetic iron oxide: SPIONs) nanoparticles, dendrimers and, micelles. Curcumin has long been thought to have anti-cancer effects.

Solvent evaporation, emulsion polymerization, and surfactant-free polymerisation have all been used to construct polymeric nanoparticles (nanospheres and nanocapsules). In case of cancer delivery of drug to a specific targeted is very essential for enhancing the therapeutic benefits of medications and decreasing harmful side effects. Hydrogel-nanoparticles are usually based on a proprietary technology that encapsulating and delivers drugs, vaccines, antigens, and therapeutic proteins using hydrophobic polysaccharides. Block-copolymer micelles are also used. Initially, drug delivery systems based on dendrimers that encapsulate drugs. Polymersomes offer features that make it possible to deliver different drugs. Conjugated Single particles- quantum dots and tumor-targeting anti-human epidermal growth factor receptor 2 MAb have been used to locate the site of tumours.

Recently, Magnetic therapy is used for cancer treatment. Magnetic nanoparticles have shown to be effective in the treatment of diseases. Photodynamic therapy (PDT) is also a safe and selective method of treatment for various types of cancer. Photothermal therapy (PTT) is generally used as a therapeutic treatment by precautionary administration, selection of laser parameters. Local light penetration for

selective targeting can be enabled by lighting. With the advancement of techniques many therapeutic procedures have been evolved for the treatment of cancer disease.

Nanoparticles are engineered for passive targeting to go across leaky arteries and the particular intra-organ pressures of malignancies. In terms of illness detection, treatment, and prevention, nanoscale technologies are transforming the scientific landscape. They might be able to turn genomes and proteomics research into widespread advantages for patients. A nanocapsule is a vesicular system which contains a pharmaceutical in a cavity surrounded by a polymer membrane, whereas a nanosphere is a matrix system in which the drug is evenly dispersed. The suitability of different types of nanoparticles simultaneously in vivo imaging and cancer treatment has been investigated. Nanoparticles can also be synthesized to detect malignant and malignant cells and provide accurate and selective drug delivery while avoiding damage to healthy and normal cells.

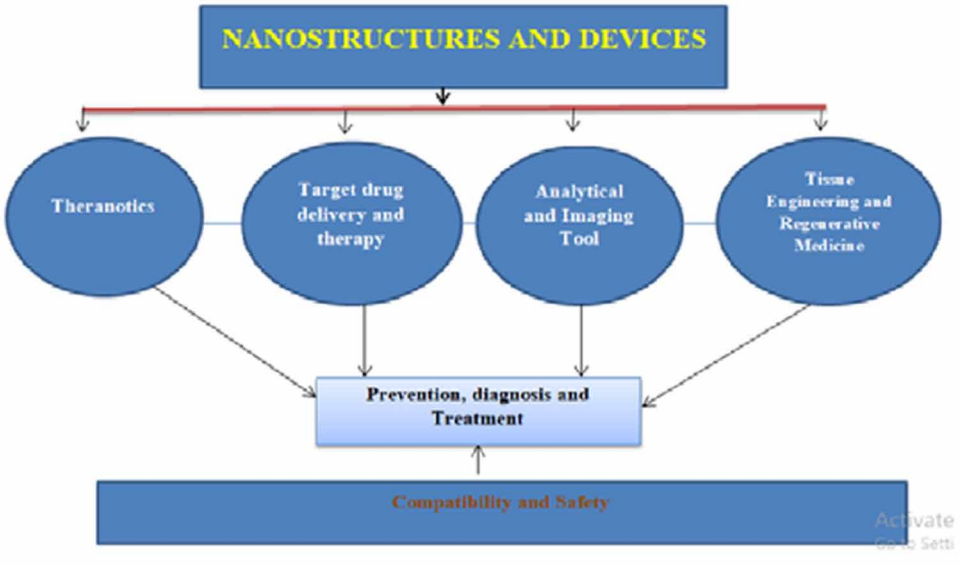
Nano delivery methods have a lot of promise for overcoming some of the barriers to efficiently targeting various types of cells. This is a unique potential to overcome resistance of drug in specific cell while also accelerating transport of drug across boundaries (e.g., BBB). However, precisely determining molecular targets and confirming that these drugs exclusively affect the organs in question remains uncertainty. It's also essential to understand what happens to drugs once they reach the nucleus and other important cellular organelles.

Nanomedicines are the applications of nanotechnology to achieve innovation in research or use of nano level measuring unit materials in the detection, prognosis, therapy and cure of disease. It makes use of the properties created by materials at its nanoscale level of 10-9 m, which often differ from the same substance at a larger size in terms of biology, physics and chemistry. Nanoparticles are important components of nanomedicine and have attracted a lot of attention as potential delivery systems of drugs for cancer diagnostics and therapy. Nanoparticles are potential therapeutic carrier system, limited oral bioavailability, and circulatory instability, insufficient tissues distribution and toxicity are some practically use challenges that have yet to be addressed. Nanoparticle will continue to open many advantages and emerge new biological applications due to their small size, customizable surface, enhanced solubility, and multi-functionality (Singh and Lillard Jr, 2009). Nanoparticles also have the advantage of becoming more suitable for intravenous delivery than larger microparticles (Bhattacharjee *et al*., 2010). The development of a number of innovative drug-delivery methods for targeting tumor has been supported by technological breakthroughs in the disciplines of biomaterials, polymer chemistry, and drug-delivery techniques (Wood *et al*., 2010). Nanotechnology has been extensively investigated and used for cancer treatment because nanoparticles can play a vital role as a drug delivery mechanism Nanoparticle-based drug delivery provides several advantages over traditional drug delivery, including greater stability and biocompatibility, increased permeability and retention effect, and precision targeting. Due to the general applicability development of hybrid nanoparticles, which integrate the characteristics of numerous nanoparticles, this type of drug-carrier system has evolved to the next level (Yao *et al*., 2020).

NANOPARTICLES BASED DELIVERY SYSTEMS

Considering their use in controlling drug release, labile molecules stabilization (e.g., peptides, proteins, or Deoxyribo Nucleic Acid), and identifying drugs for specific site, great effort is being made for the production of polymeric nanoparticles (decomposing) for delivery of drugs and engineering of tissue. In the late 1960s and early 1970s, based on acrylamide micelle polymerization first polymer micro-particles

Figure 1. Applications and Objectives of nanomedicines in biomedical Science (Patra et al., 2018).



appeared (Kreuter, 1994a). Pre-formed polymers have also been developed and investigated since then, in addition to various polymerization processes (Pitt *et al.,* 1981; Kreuter, 1994a; Barratt, 2000). These small particles made of PLA (poly lactic acid), poly-cyanoacrylate (PCA), poly (D, L Lactide), poly (D, L Glycolide) [PLG], and poly (Lactide-co-Glycolide: PLGA) have been focus on much of the nanoparticle research to date (Pitt *et al.,* 1981).

NANOPARTICLE DRUG CARRIERS: USE AND BENEFITS

Due to their capability in biological, trade and pharmacological uses, biogenic nanoparticle has received interest. Nanoparticles especially polymeric nanoparticles prepared from synthetic and natural polymers have attracted the most interest due to their easiness and stability of exterior modifications (Vauthier *et al.,* 2003; Herrero-Vanrell *et al.,* 2005). Retention and improved accessibility effect of vasculature has been shown to target nano-carriers especially inflammatory regions, tumours and antigen-targeting sites. Once packaged in the target location, hydrophobic biodegradable polymeric nanomaterials can serve as a drug depot, depending on the medication. By modifying properties of the polymer and chemicals on the surface, they can be customized to accomplish both medication release control and disease-specific features (Kreuter, 1994b; Panyam and Labhasetwar, 2003; Panyam *et al.,* 2003b). Metal nanoparticles are important in a variety of biological applications, including targeted drug delivery, bioimaging, and photodynamic treatment (Daraee *et al*., 20016, Elahi *et al*., 2018). Nanomedicines based on nanotechnology are now used in many areas of biological and biomedical (Patra *et al*., 2018) research (Fig.1).

The size and distribution of size of nanoparticles are the most important characteristics. They examine the *in-vivo* dispersion, toxicities, biological fate, and specific capabilities of different systems of delivery. They also have an impact on drug loading, drug release, and nanoparticle stability. Many researches have shown that nanoparticles exhibit a variety of properties. Particle size is an important factor in delivery

of drug through nanoparticles. The fastest and most frequent methods for assessing nanoparticle size are photon-correlation spectrometry or dynamic light scattering. The viscosity of the medium must be determined before photon-correlation spectroscopy can measure the particle diameter using light scattering properties and Brownian motion (Swarbrick and Boylan, 2002). Scanning or transmission electron microscopy is generally used to confirm the results of photon-correlation spectroscopy (SEM or TEM).

DRUG LOADING

An effective nano-delivery system should have a good drug-loading capacity, which reduces the amount of matrix materials that must be administered. There are two approaches to drug loading. The drug can be integrated during preparation of nanoparticles, according to inclusion procedure. Absorbance or Absorbance of the drug following nanoparticle creation is achieved through incubation of nano-carrier with a concentrate solution of drug. Entrapment and efficacy of loading of drug depend on solubility of drug in material of the excipient matrix (liquid dispersion agents or solid polymer), which is related to the composition of matrix, drug-polymer interactions, the presence of end functional groups (i.e., carboxyl or ester) and molecular weight in either matrix or the drug (Govender *et al.,* 1999; 2000; Panyam *et al.,* 2004). PEG is a popular polymer for formulation of nanoparticles, since it has little or no effect on loading of drug and interaction (Peracchia *et al*., 1997). Furthermore, when macromolecule, drug, or proteins encapsulated in nanoparticles are loaded at or near their isoelectric point (pI), they have the highest efficiency of loading (Calvo *et al*., 1997). Studies demonstrate that using ionic interaction between the matrix materials and the drug to increase loading of drug can be quite effective for tiny compounds (Chen and Gray., 1994; Chen *et al*., 2003).

DRUG RELEASE

When designing a delivery system of nanoparticulate, both release of drug and biodegradation of polymer must be taken into account. Release rate of drug is determined by the following means: (i) adsorbed drug desorption or surface-bound; (ii) solubility of drug; (iii) drug diffusion through the matrix of nanoparticles; (iv) erosion of the matrix of nanoparticle or degradation and (v) a combination of erosion and diffusion processes. As a result, the diffusion, biodegradation of the particle of matrix solubility and all influence the release process. Release of drug happens by diffusion or erosion of the matrix in nanospheres, where the drug is uniformly dispersed. If the drug diffuses faster than the matrix erodes, the release mechanism is essentially controlled by a diffusion process. Adsorbed drug or weakly bound to the vast surface of nanoparticles is primarily responsible for the quick initial release, or 'burst' (Magenheim *et al.,* 1993). The manner of integration clearly has effect on the releasing profile. If the medication is loaded via the incorporation method, the system exhibits a small burst effect and has sustained release features (Fresta *et al*., 1995). In such research if the nanoparticles are coated with polymer, the drug is delivered by diffusing *via* the membrane of polymer.

Solubility of drug and diffusion across the polymer membrane or inside become a decisive element in release of drug because coating of membrane acts as a barrier of drug release. Ionic interactions between the medication and the auxiliary components can potentially impact the release rate. When an entrapped drug interacts with auxiliary components, a less water-soluble compound forms, slowing

Table 1. Main classes of Nanoparticles used in drug delivery systems (Patra et al., 2018).

S. N.	Nanoparticles
1.	Biopolymeric Nanoparticles: Chitosan, Alginate, Xanthan gum, Cellulose, Liposome, Polymeric Micelles
2.	Inorganic Nanoparticles: Nonocrystals, Matellic nanoparticles, Quantom dots
3.	Protein and Polysaccharides nanoparticles

drug release and negating the burst action (Chen and Gray, 1994). When auxiliary components, such as ethylene oxide (C_2H_4O)-propylene oxide (CH3CHCH2O) block copolymer (PEO-PPO), are added to chitosan, the drug's contact with the material of matrix is reduced due to the competitive interaction of electrostatic of PEO-PPO with chitosan, resulting in an increase in release of drug (Calvo *et al.,* 1997).

TARGETED DRUG DELIVERY

An assessment on the development of systems for the delivery of nanoparticle for targeted drug delivery was published (Moghimi *et al.,* 2001). Target delivery of drug can be accomplished either passively or actively. To achieve active targeting, the carrier system or therapeutic agent must be conjugated to cell-specific ligand or a tissue (Lamprecht *et al.,* 2001). Through the EPR effect, drugs encapsulation in nanoparticles or pharmaceuticals attached to the macromolecules can also target malignancy passively. Catheters can be utilized to deliver nanoparticles to the desired tissues or organs. Localized drug-bearing nanoparticle delivery to regions of vascular restenosis, for example, could provide long-term medication release at target location on the wall of artery (Maeda, 2001; Sahoo *et al.,* 2002). Various types of nanoparticles are now being used in research and biomedical sciences (Table 1). Few nanoparticles are used for the treatment of cancer.

Natural biopolymers are also used in nanomedicine their source include Algae (Alginate, Galactans, Carrageenan), Microorganisms (Dextran, Gellan Gum, Xanthan Gum, Bacterial Cellulose). Liposome has been shown to be effective in the delivery of medicinal drugs. Drug administration specifically contact-facilitated is applied in this system, which entails interacting or binding with the desired specific cell membrane. This allows for improved lipid to lipid interaction with the monolayer of lipid of nanoparticle, allows speeds up the convective flux of lipophilic medicines (*e.g*., paclitaxel) via the outer lipid membrane of nanoparticle to specifically selected cells (Guzman *et al.,* 1996). These nano systems could be used as drug depots, with long-term release persistence and kinetics at the specific site (target location). Drug can be delivered via nanoparticles over a variety of barriers (biological) (Lockman *et al.,* 2002; Fisher and Ho, 2002). The difficulty of anti-neoplastic, anti-viral medicines, a variety of other treatments to cross the blood-brain barrier has a significant impact (BBB). The use of nanoparticles to deliver through this barrier holds a lot of promise. Nanoparticles have been shown to traverse the BBB after hyper-osmotic mannitol opens tight junctions, potentially allowing for continuous targeting of therapeutic medicines for those difficult to treat disorders such tumor of brain (Avgoustakis *et al.,* 2002). Nanoparticles coated with Tween-80 have also been proven to crossing the BBB (Beletsi *et al.,* 1999).

NANOTECHNOLOGY BASED DRUG DELIVERY FOR CANCER PATIENTS

The drug delivery to tumors is crucial for improving their effectiveness and avoiding harmful side effects. Several nanotechnology approaches, most of which are focused on nanoparticle, can improve delivery of drug in cancer.

HYDROGEL

Researchers have developed a patented method for encapsulating and delivering drugs, proteins, and vaccine antigens via hydrophobic polysaccharides called hydrogels. A newly developed technique using lipid pullulan holds great promise. These cholesterol nanoparticles are made up of four cholesterol molecules and a pullulan shell. They form a hydrophobic core that is self-aggregating as well as stabilize trapped proteins. Dendritic cells quickly absorb these particles, which trigger the immune system. Larger hydrogels, on the other hand, can also encapsulate and secrete monoclonal antibodies (Mabs).

A component of the turmeric spice known as Curcumin, has been thought to have anticancer properties. Despite this, due to curcumin's low systemic bioavailability, weak solubility and extensive medical use of this effective drug has been limited. Curcumin has been encapsulated in a polymeric nanoparticle to create "nanocurcumin," which solves this difficulty (Bisht *et al.,* 2007). Nanocurcumin also promotes apoptosis, inhibits activation of NFB (Nuclear Factor Kappa B) and by suppressing cytokine those are pro-inflammatory (IL-6, IL-8 and TNF). Through enabling for soluble dispersion, nanocurcumin has the capacity to develop the biomedical skill set of this effective medicine. Nanocurcumin research in future in preclinical *in -vivo* cancer model and illnesses which potentially applied from Curcumin's advantages is required.

MICELLES AND LIPOSOMES

Spherical super-molecular structures made out of amphiphilic copolymer block-copolymer micelles. Micelles are made up of a hydrophobic core that can store hydrophobic medications and a corona that is similar to hydrophilic brush and renders the micelles water soluble permitting poorly soluble contents of the micelle to be delivered more easily. CPT (Camptothecin) is a cancer fighting topoisomerase I-inhibitor, however due to its week solubility, toxicity and volatility, its clinical uses is limited.

Biocompatible, tailored Satirically Stabilized Micelle (SSM) has been applied as nano-carriers for Camptothecin (CPT - SSM). Because drug aggregation is avoided, Camptothecin solubilization in Sterically Stabilized Micelles is costly, yet repeatable. Furthermore, due to their nano scale measurement (14 nanometer) and capacity to extravagate *via* the leak microvasculature of tumors and inflammatory tissues, SSM comprised of phospholipids (PEGylated) are appealing nanocarrier for delivery of Camptothecin. Because of this passive targeting, medication concentrations in tumors are high while drug toxicity in normal tissues is low (Koo *et al*., 2006).

Formulations of Stealth micelle include stabilizing coronas made of PEG to reduce micelle opsonization and increase half-life of serum. DOX-encapsulated micelle formulation, NK911 is made by a copolymer of PEG-DOX conjugate poly (aspartic acid). NK911, Genexol-PM and SP1049C have all been authorized for use in clinical studies (Sutton *et al.,* 2007). Paclitaxel-encapsulated PEG- PLA for-

mulation of micelles is Genexol - PM. SP1049C is a DOX (doxorubicin)-encapsulated pluronic micelles formulation. Polymer micelle has a number of advantages over traditional technique drug of delivery, including enhanced solubility of a drug, a longer circulation half-life, selective accumulation of tumor and reduced toxicity. Furthermore, this approach still lacks tumour selectivity and the capacity to manage the release of entrapped drugs. Nano-therapy has steadily turned away from passively targeting techniques (*e.g*., micelles) and toward active targeting.

The usage of iron oxide particles especially super paramagnetic in combination with Magnetic Resonance Imaging technology (MRI) can be utilized for location the tumor and then thermally ablate it. A primary malignant tumor, GBM (Glioblastoma Multiforme) of the brain with limited effective curative choices, has been used as an example. The difficulty of getting medications over the BBB is the fundamental challenge in treating GBM. Nanoscale liposomal iron oxide formulations, on the other hand, have recently been+ proven to increase BBB penetration (Jain, 2007).

FORMULATION OF NANOMATERIAL: NANOPARTICLE ENGINEERING

Nanomaterial has been effectively engineered for the production of an advance system of drug delivery that can overcome the major issue of poor water solubility in the most promising recently available anticancer medicines, increasing their effectiveness. In order for poorly soluble anticancer medications to be easily absorbed into cancerous cells, solvent must be added. These solvents, unfortunately, not only diminish the efficacy of the medications, but also induce toxicity.

NOVEL NANOSYSTEMS

Novel Nano-systems can be programmed to change their properties and structure during the delivery process of drug, permitting for more efficient extracellular and intracellular drug administration (Wagner, 2007). This is accomplished using molecular sensor that response to biological and physical stimuli such as pH redox potential or enzyme. Two principles for tumor-targeting include targeting of active receptor and systemically targeting of passive.

Forces, physically (Ultrasound, Electric or Magnetic field, Hyperthermia or Light) may play a significant role in triggering and targeting activation of nanosystem. A biological treatment given *via* programming of nanomaterials includes plasmid DNA, si RNA and many nucleic acids of therapeutic use. The injection of multiple nanoparticles is expected to result in a high percentage of prostate tumorous cells undergoing programmed cell death. Polymer delivery, locally/DT-A nanoparticle may be applicable in the treatments of prostate cancer and benign prostatic hypertrophy. Glucosylceramide synthase converts the pro-apoptotic mediator ceramide to a non - functional molecule called glucosylceramide (GCS). Many multidrug resistance (MDR) tumours overexpress this molecule, which has been linked to survival of cell in the face of chemotherapy. (van Vlerken and Amiji, 2006; Gavas *et al*., 2021).

DENDRIMERS

Drug delivery systems based on dendrimer, were first studied for their ability to encapsulate pharmaceuticals. Controlling the release of medications associated with dendrimers, on the other hand, proved problematic. Linear polymers with dendron at all units (repeat unit) such as dendronised polymer are a new class of molecule created by recent advances in polymer and dendrimer chemistry. Another option is to conjugates/synthesis the drug to the dendrimers so that a link especially degradable can be added to regulate the releasing of drug. Through meticulous size and molecular architectural design, DOX (doxorubicin) was coupled for biodegradable dendrimer with adequate circulation time of blood (Lee *et al.,* 2006).

NANOCELLS

Encapsulation and target of chemotherapeutic drugs in nano-cells of 400 nm, which can be packed with considerable concentration of chemotherapeutic drugs of varied charge, hydrophobicity, and solubility, can reduce disturbance of drug and harmful effect of chemotherapeutic drug occurs during systemic administration (Singh and Lillard Jr, 2009; MacDiarmid *et al.,* 2007). Endocytosis, intracellular breakdown, and drug release occur when nanocells are targeted with bi-specific antibody to receptor on membranes of cancer cell. Nanocell-delivered drug doses are 1,000 times lower than the free drug dose necessary for equal tumour shrinkage. Despite administering minute doses of medication and antibody, it causes considerable growth of tumor suppress and regress in mice xenografts and lymphoma in dogs drugs (Singh and Lillard Jr, 2009). Reduced dosage is, in fact, a crucial component in minimizing systemic toxicity. This drug delivery method will be tested in clinical research.

NANOTUBES

Although, it was previously essential to connect medication molecules directly to antibodies, doing so significantly limits an antibody's targeting capabilities because the chemical bonds used hinder antibody activation.

To circumvent this constraint, a variety of nanoparticles have been studied. Many copies of specific tumor MAbs (monoclonal antibody molecules), radiation ion chelates; fluorescent probes have been covalently attached to single-walled carbon nanotubes (SWCNTs) to create tumor-targeting SWCNTs (Mc Devitt *et al.,* 2007). A new kind of anti-cancer chemical has been developed that includes combined tumor-targeting antibodies and fullerene nanoparticles (C60). Few molecules of an anti-cancer medication e.g., Taxol, can be put into this delivery mechanism (Ashcroft *et al.,* 2006).

POLYMERSOME

Polymersome, which are hollow shelled nanoparticle with unique characteristics, can transport a variety of medications. The membrane thickness of these block copolymer vesicle, their aqueous lumen and

pH-triggered release within endolysosomes were shown to be used during drug load, delivery of drug and drug's cytosolic absorption of combination from polymersome those are degradable.

According to Ahmed *et al.,* 2006, Paclitaxel and DOX have been encapsulated in polymersomes for passively administration to tumor-affected mouse. Paclitaxel can embed within the shell due to the massive polymers that make up the polymersome. It is insoluble in water. DOX is soluble is water. It remains inside internally in the polymersome's till the dissolved. If polymersomes with drugs, both are put together, they spontaneously self-assemble. Studies have demonstrated that paclitaxel and DOX in combination to tumor shrinkage in comparison to medication alone; however previously no carrier technology which can be efficiently deliver two drugs to a tumor. This strategy has a lot of potential.

QUANTOM DOTS

Using high-speed confocal imaging, quantum dots of single particle coupled to tumor-targeting anti Human Epidermal growth factor Receptor 2 (HER2) monoclonal antibodies (MAbs) were applied to find tumors (Tada *et al.,* 2007). Wilhelm *et al*., 2016 reviewed the literature on nanoparticle-based drug carriers from the previous years in, revealing that only 0.7 percent doses (median) (injected nanoparticles) was delivered to solid tumor. The limited distribution efficiency of nanotechnology has a negative impact on its translation to therapeutic applications.

Despite all of the drawbacks connected with nano-medicine, based on nanoparticle drug delivery systems remains a viable cancer treatment option. Regulatory bodies have already given their approval to few nanoparticle compositions for the treatment of cancer. These formulations have fewer side effects than the original or unmodified medications. The system development with precisely material qualities and controlled functions has taken a lot of time and effort.

Nanoparticles are formulated to attach to biological structure in tumors to surface bound ligand using recognizing of molecule in active targeting. As a result, the nanoparticles and drug-loaded nanoparticles bypass eliminating cell's nonspecific uptake, immune clearance, only accumulation of tumor cell and tissues.

CANCER THERAPIES BASED ON NANOPARTICLES

Magnetic therapy is a treatment that deeply penetrates than infrared and visible light and uses magnetic field without causing negative impact are rarely absorbed by tissues. Magnetic nanoparticles are thus promising possibilities for illness treatment. If, triggered by a magnetic field, magnetic nanoparticle (mostly contain iron oxide), can be employed for localized warming. Multilayer-assembled polyelectrolyte microcapsule of diameters of 4.6 μm was also synthesized by Carregal-Romero *et al.,* 2015.

Under light irradiation, photodynamic treatment (PDT) can destroy tumor cells by converting tumor oxygen into deadly reactive singlet oxygen (1O2). PDT is a cancer treatment approach that is both safe and selective. Although, the potential of photodynamic treatment of tumor therapy is restricted, because environment of localized tumors is hypoxic and also consumption of O_2 during photodynamic treatment. A unique oxygen self-enriched photodynamic treatment system was prepared by Cheng *et al.,* 2015 through loading of IR 780 on PFH (perfluorohexane) nanodroplets to overcome this difficulty.

PTT (PHOTOTHERMAL THERAPY)

Photothermal therapy is a type of treatment that uses light to heat (PTT). PTT involves irradiating cancer tissues with radiation of electromagnetic, which kills specific type's cells by raising temperature. The precautionary selection of laser settings and also illumination in this technology can permit for light penetration locally for precise targets.

The application of plasma nanostructures, specifically gold nanostructures e.g., gold nanoshells and AuNPs (gold nanoparticles), to take benefits of confined resonance of surface plasmon is one of the most promising approaches for PTT. Furthermore, because visible light with a long wavelength/ NIR has a deep penetration of tissue and low energy, it can be employed in PTT because it does minimal harm to other cell and tissue (Singh and Lillard, Jr, 2009).

RADIOTHERAPY (RT)

Radiotherapy (RT) is widely used therapeutic procedure of cancer which causes free radical or DNA damage in tumors. Patients, on the other hand, experience serious adverse effects. Radiation damage to normal tissue next to the tumor location is still a challenge.

ULTRASOUND (US)

Ultrasound (US) is a common tool for diagnosing and treating cancer. It can produce radiation force, form cavitation bubbles and heating local tissue, all of which are utilized to discharge pharmaceuticals from nano-composites, clean drug or/and nanoparticle of arteries of blood of tumor with increased penetration of drug.

A useful approach to eliminate Multi – Drug Resistance (MDR) with combination of negative charged nanoparticles with Ultrasound was evolved by Wang *et al.,* 2017. According to their work, cells are exposed to Ultrasound with micro-bubbles before the therapy with negative charged nanoparticles of Heparin-Folate-Tat-Taxol.

Brazzale *et al.,* 2016 utilized folic acid to prevent opsonization and stabilize the colloid in vivo, (to adorn gold nanoparticles surface-coated with PEG). As Ultrasound sensitizers, the nanoparticles can operate particularly on HCT-116 and KB cells, inhibiting cell growth by producing reactive oxygen and enhancing necrosis of cell.

USE OF COMBINATION OF TERAPY FOR TREATMENT OF CANCER

Despite the fact that nanoparticle-based cancer therapeutics have shown fascinating therapeutic efficacies, researchers are still looking for the perfect synergistic impact by combining two or more therapy modalities. Combination therapy options have considerably better anti-tumor activity.

PTT AND PDT COMBINED THERAPY

Modification of peptide increased GSPID development in glioma cells substantially. GSPID displayed enhanced chemo-photothermal synergistically therapeutic targets as well as good drug release capabilities, making it an ideal drug delivery system for glioma treatment. However, this therapeutic treatment can avoid by invasive and frequent dosing and improving compliances of patients. pRGO (polydopamine-functionalized Reduced Graphene Oxide) with MS (Mesoporous Silica) coat was constructed by Shao *et al*., in 2017. Polydopamine-functionalized reduced graphene oxide was again formulated with HA (Hyaluronic Acid) to form pRGO@MS (DOX)-HA Nanocomposite, a multimodal system of therapy and a system of drugs delivery of multifunctionally. Nanoparticles have a synergistically targeted chemo-PTT effect. The functionalized biomolecule was synthesized as biologically compatible biopolymer-coated RGO nanosheets in one step using mussel-inspired dopamine as the reducing reagent. MS (Mesoporous silica) was then coated with polydopamine-functionalized reduced graphene oxide to increase DOX loading and to allowing an interface (active) for modification with hyaluronic acid, the targeting moiety (Singh and Lillard Jr, 2009).

In 2017 Feng *et al.,* developed a NIR-responsive and magnetic tumor-targeting system for delivery of drug. This technology, in a short time, can construct improved photo-thermal transduction efficiency and DOX is simultaneously discharged due to photo-hyperthermia with the control of spatiotemporal of irradiation of NIR.

COMBINED THERAPY WITH CHEMOPHOTODYNAMICS

One of the scariest cancers is advanced colorectal cancer. Traditional immunotherapies, such as antibody-based suppression of the PD-1/PD-L1 axis, remain first most promising, but their sustained response rate is relatively low. He *et al*., (2016) produced NCP (nanoscale coordination polymer) core-shell nanoparticles for PDT, chemotherapy and PD-L1 checkpoint blockade therapy of cancer, which can contain oxaliplatin in core and the photosensitizer pyropheophorbide-lipid conjugate (pyrolipid) in the shell (NCP @ pyrolipid). NCP @ pyrolipid has a controlled drug release and circulates for a long time.

UCNs that were membrane engineered with bovine serum albumin-poly (caprolactone) BSA-PCL were introduced by Dong *et al*., 2016 to create a system of combination of imaging of tumor cell, chemotherapy and photodynamic treatment. A protein-polymer bio conjugate-coated multifunctional up conversion Nano system is at the core of the UCN. In the customized amphiphilic protein-polymer bioconjugate shell, the anticancer drugs ZnPc and DOX are co-loaded. The UCN core of this structure transforms NIR light to visible light, permitting for cell fluorescence imaging, while activated ZnPc produces harmful ROS, allowing for photodynamic treatment.

COMBINED IMMUNOTHERAPY AND PHOTOTHERMAL THERAPY

By combining adjuvant nanoparticle-based PTT alongside checkpoint-blockade immunotherapy, the immunotherapy and PTT combined treatment method can limit tumor spread and destroy primary tumors. A nanoplat-form has been created for the dual imaging and simultaneously functionalized PDT/PTT therapy.

CHEMOTHERAPY AND PTT TREATMENT IN COMBINATION

Attribute to systemic side effects and limited efficiency of treating strategies, therapy effect and patient compliance in malignant glioma is inadequate. Wang *et al*., 2013 used a unique multifunctional drug delivery system to targeted therapeutic procedure of combine chemo-photothermal for Glioma in combination of unique adaptive system of delivery of drugs. Graphene nanosheet changed with a targeting peptide and covered with GSPI (Mesoporous Silica) was successfully produced. GSPID (DOX-loaded GSPI system) demonstrated pH-responsive, long-term release and excellent heat-simulative properties. The observations of cytotoxicity assays revealed, Glioma cells treated with the two therapeutic treatments exhibited a more fatality rate in comparison to any of administered with only Chemotherapy or Photothermal Therapy.

For the production of cancer vaccines, tumor lysate (whole tumor cell lysates TCL) has been employed as a tumor antigen. In 2016 Shi *et al*., developed CTS NPs called Chitosan nanoparticles with Man (Surface Mannoses) moieties (Man-CTS NPs) for the specialized target of dendritic cell. Zhen *et al.,* 2017 described a nanoparticle-based photoimmunotherapy (PIT) method. A compact nanoparticle protein scaffold connected to a FAP-specificity specific region was used as the photosensitizer carrier and ferritin was used as the photosensitizer (scFv).

PTT AND DIAGNOSIS

To increase the success of cancer treatment, initial illness detection or diagnosis, as well as specific therapeutic impact observing on lesions after therapy, are crucial. Combining diagnostic and treatment has become a popular cancer treatment approach. Liu et al., 2016, developed ultra-small Cu3BiS3 nanodots (NDs), single-phased ternary bi - metallic sulphide nanomaterials that are effective, degradable, and safe nanomedicine for PTT-guided MSOT and X-ray CT. Due to the remarkable of light absorption of NIR and photo thermal stability of the reduced graphene oxide layer, Moon *et al*., 2015 provided a system of reducing graphene oxide-coated gold nanorods (r-GO-AuNRs) exhibiting considerably improved photoacoustic (PA) performance. The efficacy of different types of nanoparticles for simultaneously in vivo imaging and treatment for cancer has been examined.

CONCLUSION

Nanoparticles have the potential to be an important drug delivery technique. Nanotechnology has been intensively explored and employed for cancer treatment. Despite the fact that nanoparticles have aroused high hopes for cancer diagnosis and treatment, hurdles remain, particularly in terms of finding practical application in live beings. Recent research efforts are, nevertheless, more than ever before resolving many difficulties and also attaining effective cancer nano-therapy.

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Chapter 23

Role of Herbal Bioactive Compounds as a Potential Bioavailability Enhancer for Active Pharmaceutical Ingredients

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ABSTRACT

Bioactive compounds of plant origin are used all over the world because of their positive impact on human and animal health and because of their beneficial, specific properties. The most popular bioactive compounds beneficial to health have been identified and defined earlier. Others are yet to be discovered. In particular, the most common biological activities of these compounds were indicated, such as antial-

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lergic, antidepressant, antidiabetic, anti-inflammatory, antimicrobial, antioxidant, antitumor, antiviral, antithyroid, anxiolytic, to cardioprotective, hepatoprotective, and flatulence-inhibiting effects. The beneficial properties of bioactive compounds may be associated with substances like alcohols, terpenoids, phenolic antioxidants, and rosmarinic acid, which are present in several medicinal plants. The updated review considers the physiological, botanical, phytochemical, and medical aspects of herbal bioactive compounds as well as their therapeutic properties, with a focus on their health benefits and the potential use of nutraceuticals.

INTRODUCTION

Biological plant compounds are now popular and studied by scientists in Europe and around the world. Medicinal herbs and plants are a rich source of numerous substances with a broad spectrum of activity. Bioactive compounds from herbs are widely used for medicinal, therapeutic and cosmetic purposes. Plants with a health-promoting effect have been used since antiquity, and now, thanks to the use of research methods, it is possible to thoroughly comprehend the mechanisms of influence of the complexes present in them. This influences the increasing use of plant materials in modern phytotherapy. Secondary substances include, among others: tannins, alkaloids, flavonoids and phenolic compounds (Verma *et al.,* 2015; Abdel-Naime *et al.,* 2019; Luta *et al.,* 2020). The great variability of these bioactive fragments makes them promising candidates for the production of pharmaceuticals, nutraceuticals and cosmeceuticals (Acevedo *et al.,* 2013; Abdel-Naime *et al.,* 2019). In recent years, there has been increasing uses in bioactive compounds as substances that reduce the risk of non-communicable diseases. Herbal teas and drinks, consumed as part of a balanced diet can improve a person's overall health. They are an excellent natural source of bioactive compounds such as alkaloids, flavonoids, coumarins, carotenoids, phenolic acids, lignin's, lignans, oxylipins, polyacetylenes, saponins, terpenoids and others (Awad *et al.,* 2009, Verma *et al.,* 2015, Chandrasekara & Shahidi 2018, Abdel-Naime *et al.,* 2019, Benarfa *et al.,* 2020, Sharifi-Rad*et al.,* 2021a; Sharifi-Rad*et al.;* 2021b). The available literature provides information on the beneficial biological activities of natural biological compounds. Herbs and medicinal plants may contain plant pathogens such as mycophytes that reduce their quality and cause serious health problems (Chandrasekara & Shahidi, 2018; Sharifi-Rad*et al.,* 2021a; Sharifi-Rad*et al.,* 2021b). Fungi species such as *Alternaria* sp., *Fusarium* sp. or *Penicillium* sp. May also produce secondary metabolites, posing a serious threat to animal feed that require decontamination (Sharifi-Rad et al. 2021a; Heinrich *et al.,* 2020). Due to the known pharmacological activity of medicinal plants, this chapter highlights a fresh look at chemical composition, pharmacological properties, pharmaceutical and therapeutic use, and safety profiles in order to guide future work and assess their clinical value.

METHODOLOGY

To demonstrate the role of bioactive substances in plants and to fully assess the context, a quantitative analysis of the literature was conducted, which shows great interest in them due to their highly beneficial properties and pro-health effects. The search for bioactive compounds and their correlation with health was conducted using the Scopus database to search bibliometric data by means of a keyword search (bioactive compounds and health) (Scopus, 2022). The papers and books that mentioned these words, their derivatives in the paper title, summary and keywords have been known in the search approach

Table 1. Phenolic compound of siderite condensate soaked in water at 100°C for 30 or 10 minutes

Phenolic compounds	Plant elements	Phenolic acids [g g^{-1}DM]
Phenolic acids		
Protocatechuic	flower	0.21
p-Hydroxybenzoic		-
P-Vanillic		1.570
Ferulic		0.060
P-Coumarin	seed	0.251
Caffeic	leaf	0.607
Flavonoids		
Catechin	leaf	0.210
Rutin		0.880
kaempferol		1.058*
Quercetin	flower	1.903
a-Isorhamnetin		1.528*

Source: own based on Chandrasekara & Shahidi (2018), USDA (2019). *Steeping for 10 minutes

(Software, VOSviewer, 2021). The functions of the Scopus internet platform called Analysis and Create a citation report were used for basic analyzes. Then, the terms used in paper titles, highlight, graphical abstract, summary and keywords of the publication were examined by using the VOSviewer software (2021). As a result of the search, two hundred and eight publications for the period from 1979 to 2022 were considered.

CHEMICAL COMPOUNDS IN HERBAL PLANTS

Medicinal plants, certain spices, herbal teas, as well as fruits, vegetables, oilseeds, pulses, and cereals were considered the main sources of plant-derived antioxidants, essential in preventing oxidative loss in the human body when the body's internal antioxidant protection systems are threatened by overexposure to free energy (Chandrasekara & Shahidi, 2018, Sharifi-Rad *et al.,* 2020, 2021a, 2021c, 2021d; Messaoudi *et al.,* 2022).

Antioxidant Compounds in Herbal Plants

Phenolic Compounds

Regarding the polyphenol profile of methanol extracts from whole plants *M. officinalis,* Awad *et al.* (2009) isolated the following organic acids: rosemary, ursolic and oleanolic. Astani *et al.* (2012)was extracted from the dried leaves of *Mellilotus officinalis* the acids as: coffee acids, p-coumaric and rosemary. Active antioxidant compounds and nitric acids A and B, in turn, were found and also quantified by Kamdem et al. (2013). In lemon balm leaves extracted with 70% ethanol, Javad Sharif *et al.* (2021a)

determined using liquid chromatography and mass spectrometry (LC-MS) such compounds as: rutin, isovercitin, quercetin, kaempferol and gallic, chlorogenic, coffee, rosemary and ellagic acids. Recently from *Thymus vulgaris* leaves (*Lamiaceae*) leaf extract, by LC-MS, was isolated the following compounds: ethyl caffeate, luteolin 3-O-β-D-glucuronide and the following organic acids: succinic, quinic, chicory, citric, danshensu, malic, tartaric, caftaric, coffee, lithospermic A, salicylic and 3'-O-(8''-Z-caffeoyl) rosemarinic acid (Chandrasekara & Shahidi 2018, Aubert *et al.,* 2019). Binello *et al.,* (2017) used microwave extraction (MAE) and ultrasound protocols to selectively extract polyphenols from *M. officinalis*. These authors found that rosmarinic acid turned out to be the most critical part of phenolic fractions, and ethanol was a good solvent in both USG and MAE procedures. E.g., Indian pennywort, *Apiaceae* family, raw material: dried plant, health benefits: anti-cancer – increases the activity of antioxidant enzymes (Chandrasekara & Shahidi 2018; Sharifi-Rad*et al.,* 2021c, 2021d; Messaoudi *et al.,* 2022).

Phenolic Acids

In herbal plants, phenolic acids are found in bound form as esters and glycosides, included mostly in the lignin's and tannins. Phenolic acids in their structure have hydroxyl and carboxyl group. The most common in medicinal plants are hydroxyl derivatives of benzoic and cinnamic acids. The composition of hydroxybenzoic acids is shown in Table 37.1. In medicinal and spice plants, phenolic acids occur in a bound form, in the form of esters and glycosides, which are included in lignin's and hydrolysing tannins. Herbal drinks have many phenolic acids (Chandrasekara & Shahidi, 2018; Sharifi-Rad *et al.,* 2021d; Messaoudi *et al.,* 2022).

Flavonoids

Flavonoids are among the most important polyphenols, which, due to the diversified chemical structure, play a number of roles functions in plants. These compounds are found in vegetables, grains, tree bark, rhizomes, stolons, roots, flowers, and fruits, as well as in tea and wine. These natural raw materials and plant products are known to have beneficial effects on health. Flavonoids are currently considered an essential ingredient in a diversity of nutraceutical, medicinal, and pharmaceutical applications. These functions are attributed to their anti-mutagenic, antioxidant, anticancer and anti-inflammatory, characteristics. Due to their chemical structure, they can be divided into anthocyanidins, flavones, flavanols, flavonols, flavanones and isoflavones (Acevedo *et al.,* 2013; Chandrasekara & Shahidi, 2018, Luta *et al.,* 2020). Flavonoids such as apigenin and isorhamnetin, catechin, quercetin, kaempferol and rutin are components of the water infusions of Siderites condensate leaves, flowers, and seeds. For example, an infusion of flowers prepared within 10 minutes has about 15 mg of isorhamnetin in 1 g of dry weight (Chandrasekara & Shahidi, 2018; Arshad *et al.,* 2020).

Lignans

Lignans consist of two conjugated phenylpropanoid parts related by fundamental carbons of their on the side chains (Luta *et al.,* 2020). Secoisolariciresinol, lariciresinol, matairesinol, pinorezynol and syringarezinol are lignans present in plants and most commonly consumed by humans. Lignans are considered important in together the avoidance and treatment of cancer. Also, they are characterized by other, positive healthiness effects, like: antimutagenic, antiestrogenic and anticancer. The positive

effect of plant lignans and their derivatives on health has been proven *in vitro* and *in vivo* tests. Both secoisolaricresinol and matairesinol are very easily converted by the intestinal microflora in the human intestine into lignans, enterodiol and enterolactone. They have an extraordinarily strong antioxidant and estrogenic effect (Luta *et al.,* 2020; Software, VOSviewer, 2021).

Lignin's

Lignin's are created as a result of the polymerization of a combination of three monolignols (Messaoudi *et al.,* 2022). Lignin's are a polymer whose monomers are organic compounds derived from phenolic alcohols. They are acrylic aldehyde, dihydroconiferyl alcohol, p-hydroxy-3-methoxybenzaldehyde, synapaldehyde, 5-hydroxyconiferyl alcohol, tyramine phebruate and other compounds that are makeup lignin. This by-product goes a long way it is used for energy and medical purposes. The potential hidden in the structure of lignin creates opportunities for broader directions of development, both scientific and research and industrial. There are options for lignin in the treatment of diabetes, viral infections, obesity, cancer, and thrombosis. Lignin's can also be used to prepare nanoparticles for the delivery of various drugs, and it is also possible to use them in photoprotection (Sharifi-Rad *et al.,* 2021c; Christensen, 2020).

Tannins

Tannins, compared to other polyphenolic compounds, are little known, but plant extracts containing this have been used in folk and traditional medicine. These compounds fall into two groups: hydrolysing (gallotannins and ellagotannins) and non-hydrolysing, also known as proanthocyanidins. In terms of chemicals tannins are esters of sugars and phenolic acids or are polycondensates of flavonoids (flavan-3-ols) (Messaoudi *et al.,* 2022). Vegetable tannins can significantly improve the quality of meat and milk and the oxidative stability of animal products, which has a considerable effect on human fitness and health. The mechanism of the anti-inflammatory action of tannins was analysed (Sharifi-Rad *et al.,* 2021; Christensen 2020). The biological activity of tannins is related to interact enzymatic, receptor proteins and transcription factors. The toxicity of tannins results from their interaction with digestive enzymes and the influence on the bacterial flora of the gastrointestinal tract, or the chelation of iron ions, which may significantly influence the development of anaemia. In addition, tannins handle causing the astringency effect when consuming foods rich in these compounds. This is due to the interaction of tannins with plant proteins and taste receptors present on the surface of the tongue (Sharifi-Rad *et al.,* 2021d; Messaoudi *et al.,* 2022). Despite the influence of tannins on the human body, these compounds show a number of pro-health properties: anticancer, anti-inflammatory, antimutagenic, antiplatelet, antibacterial, and also antiviral. The inhibition of tyrosine kinase, metalloproteinases and vascular endothelial growth factor by tannins underlies their antiproliferative activity. In turn, inhibition the activity of various proteins involved in the development of pro-inflammatory reactions (e.g., xanthine oxidase, cyclooxygenase two and induced nitric oxide synthase) manages anti-inflammatory properties (Christensen, 2020).

Coumarins

Coumarin is chemically a lactone of ortho-hy-droxy-cis-cinnamic acid, also known as coumaric acid. Food includes simple coumarins, furanocoumarins and pyranocoumarins (Luta *et al.,* 2020; Christensen, 2020). Some herbs or spices used as nutraceuticals have natural coumarin compounds in significant

amounts. Recently, there has been a lot of interest in these compounds due to their general and specific toxicity. Many natural coumarins have been evaluated for the pharmacological properties, including neuroprotective, antioxidant, anti-inflammatory, antidepressant, and anticancer properties. Several natural coumarins have been used in drug development, such as warfarin (Astani *et al.,* 2012; Christensen, 2020). Coumarin derivatives as natural chemical compounds (often in the form of glycosides) are used in medicine. The richest source of structures having the system of coumarin, and its derivatives are plants (plants from the celery family (*Apiaceae*), madder (*Rubiceae*), rutaceae (*Rutaceae*), olive (*Oleaceae*), Fabaceae (*Fabaceae*), Asteraceae (*Asteraceae*), Chestnut (*Hippocastanaceae*) and nightshades (*Solanaceae*), as well as bacteria of *Streptomyces* and *Aspergillus* strains). Folk medicine has long used the healing properties of plants, attributed in part to or all the coumarins present in them. An example is lovage (*Levisticum officinale*), which is used in the case of stomach disorders or menstrual disorders, but also coughs or as an early abortion measure, and has coumarin, umbeliferon, apertin and bergapten. Many coumarin derivatives are also found in plants such as *Ruta graveolens*, *Angelica archangelica*, and the marsh gorse (*Peucedanum palustre*) or gorse (*Peucedanum praeruptorum*) (Astani *et al.,* 2012, Luta *et al.,* 2020; Christensen, 2020).

Terpenes

Terpenes and derivatives of terpenoids are secondary metabolites, derived from isoprene (2-methyl-butadiene) (Sharifi-Rad *et al.,* 2020). Depending on the quantity of isoprene components, the organic compounds of terpenes divided into the categories: isopropenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterpenes (C_{25}) and the politerpenes. The assembly of triterpene composites includes triterpenes and sterols, which accumulate in plants like saponins (glycosides). Saponins are plant chemical compounds belonging to the group of glycosides, i.e., substances derived from sugars. These are plant compounds with foaming properties, they were used as a soap substitute, for example for washing. Saponins, apart from washing properties, also have valuable health and healing properties. They have a diuretic, expectorant effect, increase the secretion of mucus, support the processes of absorption of nutrients from the intestines into the blood, have an antibacterial, protozoicidal, antiviral, and anti-inflammatory characteristics. In addition, stimulate the secretion of gastric juices, bile, and intestinal juice, supporting digestive processes, lowering the level of "bad" cholesterol, increasing the digestion of fats, but large doses administered orally have an emetic effect. Saponins called sapogenin is secondary metabolites with surface-active properties. It is now known that saponins, apart from washing properties, also have valuable health properties and broad healing effects. For these reasons, this substance has been used in the treatment of many diseases. Saponins are diuretic and expectorant intensify the secretion of mucus, support the absorption of nutrients from the intestines into the blood, have, antibacterial, antiviral, protozoicidal and anti-inflammatory properties, stimulate the secretion of gastric juice, bile and intestinal juice, supporting digestive processes, reduce the level of "bad" cholesterol, increase the digestion of fats large doses administered orally have an emetic effect (Astani *et al.,* 2012; Sharifi-Rad *et al.,* 2020; Christensen, 2020).

Carotenoids

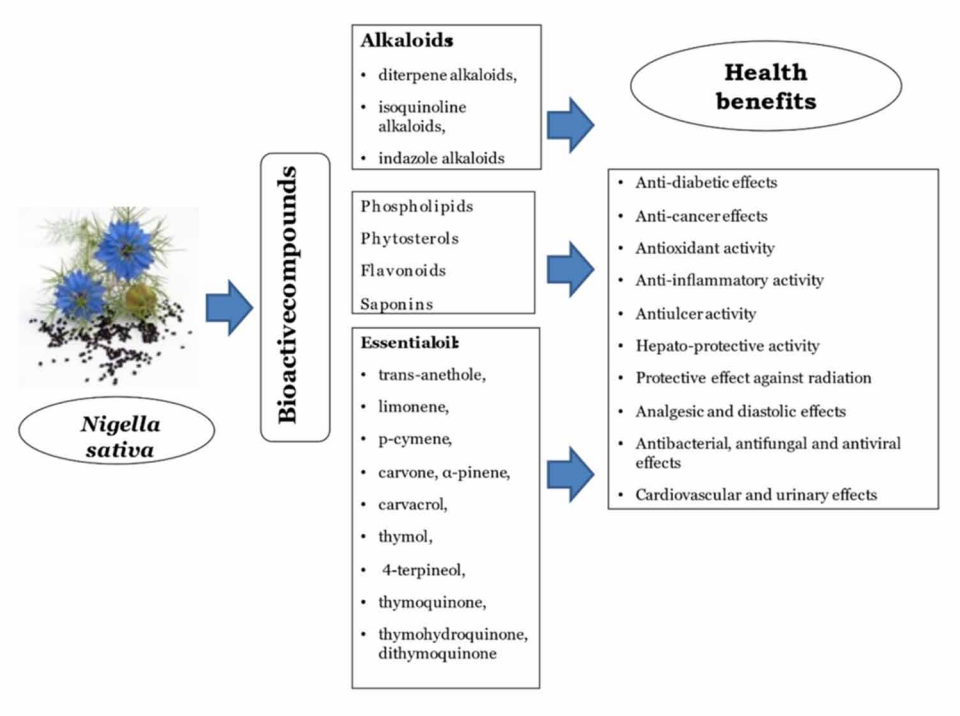
Carotenoids (CT) usually are yellow, red, or orange pigments. These colors ordinarily show changed types of Carotenoids and different bioactive properties due to their distinctive structure, plus antioxidant and

anti-inflammatory properties. Around 750 Carotenoids occur in nature, and they are available in plants as well as animals (Acevedo *et al.,* 2013; Benarfa *et al.,* 2020). They are characterized by provitamin A and antioxidant properties. They belong to hydrocarbons with a minimum of forty carbon atoms with eight isoprene units. The structure of carotenoids able to be cyclized at single or together ends and is characterized by a different amount of hydrogen atoms or by having a functional group that has oxygen, the latter being called xanthophylls. Analysing the chemical structure of these compounds, it can be said that it is a system of eleven conjugated double bonds, thanks to which they can be classified into the group of polyisoprenes. They are insoluble in water, but very soluble in fats, with which they often form esters. Due to the differences in the polyisoprene chain, carotenoids are branched into two classes. The main of them are compounds having only carbon and hydrogen atoms with the formula $C_{40}H_{56}$. These are most often all-trans isomers, thermodynamically more stable. The change of the isomerism to cis-trans is possible only at elevated temperature and / or with intense radiation. Isomers yew is found in vegetables and fruits (Benarfa *et al.,*2020). Due to this structure, carotenoids are less polar substances, they absorb radiation with a higher wavelength. The first group of carotenoids also includes compounds that have short carbon chains but have a central carotene fragment with four methyl groups (e.g., bixin). Whereas the second group of compounds has at least one oxygen atom, e.g., in a hydroxyl group, carbonyl, carboxyl or hydroxymethyl. The second group of carotenoids is called xanthophylls. These relationships are common in nature, they are similar both chemical, biochemical, and physicochemical. Xanthophylls are more compounds polar, absorbing radiation with lower wavelengths than other carotenoids. Due to this structure, carotenoids are less polar substances, they absorb radiation with a higher wavelength (Abdel-Naime *et al.,* 2019). The first group of carotenoids also includes compounds that have short carbon chains but have a central carotene fragment with four methyl groups (e.g., bixin). Whereas the second group of compounds has at least one oxygen atom, e.g., in a hydroxyl group, carbonyl, carboxyl or hydroxymethyl. The second group of carotenoids is called xanthophylls. These relationships are common in nature, they are similar both chemical, biochemical, and physicochemical. Xanthophylls are more compounds polar, absorbing radiation with lower wavelengths than other carotenoids (Sharifi-Rad *et al.,* 2021d). The most common organic chemical in foods include β-carotene, alpha-carotene, and lycopene (carotenes), and lutein, astaxanthin, cryptoxanthin, zeaxanthin, canthaxanthin and fucoxanthin (xanthophylls). The main active carotenoids of provitamin A are β-carotene, α-carotene and cryptoxanthin. Carotenoids are naturally occurring pigments that play a significant role primarily in neurodegenerative diseases in preventing brain disorders (Sharifi-Rad *et al.,* 2020, 2021d).

Polyacetylenes

Among the plant compounds with potential action alkaloids, including isoquinoline and steroid alkaloids as well as alkaloids from the *Amaryllidaceae* and *Colchicum* families, were antibacterial and antifungal. They are in this group coumarins, quinones, polyacetylenes, saponins and plant compounds from other chemical groups. Polyacetylenes are a set of bioactive compounds in which the bonds between carbon atoms are formally alternating double and single bonds (so-called conjugated bonds). Polyacetylenes are formed during acetylene polymerization, during which triple bonds transform into double bonds, creating bonds between later molecules: n CHºCH ® - (CH = CH) (Kamdem *et al.,* 2013). In the studies of Ouakouak et al. (2021). Leaf-derived essential oils (EO) were shown to have low radical scavenging activity using the two antioxidant tests DPPH and ABTS. Moreover, EO was characterized by a strong inhibitory effect on colon cancer and moderate inhibition of hepatocellular carcinoma cells.

Figure 1. Diagram of the interaction of the widely essential bioactive compounds from medicinal plants and their relationship with biological activity.



Oxylipins

Oxylipins are a family of oxidized natural products, obtained from fatty acids in processes with at least one oxygen-dependent oxidation stage. Oxylipins manage the signalling of molecules resulting from the oxidation of polyunsaturated fatty acids (PUFA). They are important cell mediators, and their action is often similar to that of local hormones (Verma *et al.,* 2015). They are derived from polyunsaturated fatty acids (PUFAs) via COX (cyclooxygenase) enzymes, LOX (lipoxygenase) enzymes or cytochrome P450 peroxygenase. These compounds perform various physiological functions in plants. They take part in the defence reactions of plants to biotic stress. Bioactive acetylene oxylipins (C17, C18) in medicinal plants they stand up by anticancer, cytotoxic, and anti-inflammatory properties. These compounds are widespread in plants of the *Apiaceae,* and *Asteraceae* families and have an effect on the inhibition of the cell cycle and on the elimination of cancer cells that have been used up or damaged and therefore could harm the proper functioning of the body. They also exert a chemopreventive result on the growth of cancer. Oxylipins have a strong effect on the improvement of fungi. The use of oxylipins as potential food preservatives is under consideration (Christensen, 2020).

BIOLOGICAL ACTIVITY OF MEDICINAL PLANTS

This section describes the basic potential functions of substances that increase the bioavailability of active pharmaceutical ingredients. One of the important intensity bioavailability enhancers for active pharmaceutical and therapeutic constituents are herbs, which do not have activity on their individual, but when used together thanks to active pharmaceutical ingredients (APIs), they can increase their efficiency, effectiveness and bioavailability. Herbal enhancers are instrumental in providing biodiversity and increasing the biological value and effectiveness of many drugs. For a substance to be biologically active, it should positively affect the human body, individual cells and tissues. These substances are important for normal human progress and growth and have confirmed health advantages and benefits. In addition, they influence a smoother course of many diseases. In the classical sense, bioactive ingredients are not nutrients (Embuscado, 2019; Kumar *et al.,* 2019).

Bioactive Ingredients

Bioactive ingredients are not necessary for life, however they have essential functions because they affect biological or cellular functions, which result in useful health effects, change the risk of disease, not prevent disease, and function as enzyme inducers and inhibitors, receptor activities' inhibitors, as well as inducers and inhibitors gene appearance (Sharifi-Rad *et al.,* 2020).

The biological properties and characteristics of medicinal plants (MP) are related to the existence and action of bioactive compounds as: rosmarinic acid and terpenoids. Hugh essential bioactive compounds isolated from herbs and their interaction with biological activity were given in Figure 1.

Bioactive compounds are important nutrients that are commonly found in lesser amounts in vegetables, fruits and herbs and are known for their behavioral, immune and physiological properties. Many bioactive compounds have been recognized. These include lycopene, anthocyanins, carotenoids, polyphenols, flavonoids, tannins, terpenoids, saponins, taurine, and phytoestrogens (Kumar *et al.,* 2019). Bioactive substances can be divided into many classes based on their function, compound structure and which influence the physiological and metabolic functions of the organism (they strengthen, weaken or modify). It is essential to note the various health benefits of these substances. They block low-density lipoproteins, have antioxidant and anticancer effects, improve cardiovascular, joint, gastrointestinal, and immune system strengthening (Embuscado, 2019).

As shown by epidemiological studies, e.g., in India, where spices are consumed in large amounts every day, the incidence of cancer is much lower than, for example, in Canada, where spice use is much lower (Kunnumakkara *et al.,* 2018).

Phenolic compounds, found naturally in plant products, are a component of the human feeding, these later have an aromatic cycle containing one or other hydroxyl compounds and their structure varies from phenolic to great molecular. The most common are simple phenols, phenolic acids, coumarins, ñavonoids, lignans, xanthones, anthraquinones, stilbenes, the most numerous of which are phenolic acids and ñavonoids. These compounds have many physiological properties, like antioxidant, antiallergic, antiallergic, anti-inflammatory, antiatherosclerotic, antiatherosclerotic, antibacterial and cardioprotective effects (Kumar *et al.,* 2019; Kulbat 2016; Albuquerque*et al.,* 2021).

These compounds, the most abundant in the group of phytochemicals, has serious role in the physiological and morphological activities of plants, especially in their growth and reproduction. They also protect against predators and pathogens, and they impart color and sensory features to fruit and vegetables

(Kulbat, 2016). In herbaceous plants there are hydroxyl derivatives of phenolic compounds naturally produced by plants (Kumar *et al.,* 2019; Kulbat, 2016). Phenolic acids have various pharmacological properties, e.g., they have anti-inflammatory, antipyretic, antibacterial, antiviral, antifungal, immunostimulant and choleretic activity (Kumar *et al.,* 2019; De Araújo *et al.,* 2020).

Flavonoids were conceded significant of antioxidants activities for of their great redox potential, which enables them to function as reducing agents. Consuming copious amounts of flavonoids helps prevent cancer and heart disease (Albuquerque *et al.,* 2021; Ignat *et al.,* 2011; Takshak 2018; Takshak 2018; Câmara*et al.,* 2021). These compounds show antitumor, anti-inflammatory and antiviral activity against DNA and RNA viruses (Panche *et al.,* 2016). The antiviral activity of ñavonoids has been demonstrated at various stages of viral infection. Flavonoids, because they can block the process of attaching and penetrating the viral particle into the host cell. In some cases, these compounds can modify the structure of the virion, which interferes with the flattening of the viral particle. Flavonoids can also be inhibitors of the initial stages of replication of the viral genetic material. They can block transcription and translation of viral proteins. Antiviral activity of ñavonoids is also related to the interaction of these compounds with cellular factors and modulating the host's immune system (Lalani & Poh,2020). The role of phenols and ñavonoids relates to the structural, supportive or protective action of tissue, involved in protection strategies, like attractants for pollinators and as allelopathic agents against ultraviolet radiation (Jaganath & Crozier, 2010).

Anthocyanins belong to the class of flavonoids and are water-soluble vacuolar pigments, appearing purple, blue or red based on their pH. They are found in all plant tissues, including (leaves, fruits, flowers, stems, and roots (Albuquerque *et al.,* 2021). Anthocyanins donate hydrogen molecules to vastly reactive radicals, thanks to which they have antioxidant properties and prevent their further formation. These are compounds that can be used to color food. Because they are water soluble, this allows them to easily integrate into aquatic food systems. Thus, they are helpful in obtaining additional health benefits in colored foods (Albuquerque *et al.,* 2021).

Plant secondary metabolites are characterized by biogenetic diversity and diverse structures. This determines their multidirectional biological activity. The secondary metabolites of alkaloids are composed of one or more amino acids (for example lysine, tyrosine or tryptophan). Alkaloids are the most diverse and medically important components of plants, although they have a bitter taste. They are colorless, optically active, crystalline or liquid at average temperature. Cultivated plants are the main source of alkaloids. About 20% of plant species contain these substances. About 150 of the more than 12,000 alkaloids are recognized in this group. Alkaloids are found in plants as salts of organic acids e.g., acetic, lactic, malic, oxalic, tartaric, tannic. Alkaloids are highly toxic as their key role is to protect plants from microorganisms, herbivores and insects (Zotchev, 2013; Saboon *et al.,* 2019). Based on their chemical structure (heterocyclic ring), biosynthesis pathway or biological properties, these compounds have been divided into more than twenty groups. Tropane, indole, imidazole, purine and pyrimidine alkaloids are distinguished (Bribi, 2018). Alkaloids can exhibit antibacterial, anticancer, antiviral and antifungal activities. Naturally occurring alkaloids, as well as their synthetic derivatives, are now a rich source for the design of new effective drugs (Adejoke *et al.,* 2019).

Carotenoids were found in abundance in certain fruits and vegetables and were known with fat-soluble pigments. The sources of carotenoids in the human food are mainly: β-cryptoxanthin, lycopene, lutein and β-carotene, but 750 members of this group have been identified (Degrou *et al.,* 2013; Meybodi *et al.,* 2017). They are beneficial to our health as these compounds are converted into vitamin A or retinol. β-carotene is the most active basic provitamin A, but when consumed as a separate supplement, it

may have a detrimental effect (Hernández-Almanza *et al.,* 2016; Salehi *et al.,* 2019a). Carotenoids not only exhibit antioxidant properties, but they also help to modify the cell cycle, apoptosis, cell signaling pathways and support the immune system (Gloria *et al.,* 2014; Karadas *et al.,* 2016; Kim *et al.,* 2016).

Terpenoids are produced by plants and so far, over 55,000 have been identified. They are added to food as vitamins, flavors and fragrances. Terpenoids have antibiotic, antibacterial, antitumor, antiviral and immunostimulatory properties, therefore they are also used for therapeutic purposes. Their role in the plant is, inter alia, on regulating growth and development as well as participation in interactions between plants and the defense response to pathogens or pests (Blande *et al.,* 2011; Luan *et al.,* 2013).

Lycopene is an acyclic carotenoid that is not a precursor to vitamin A. This compound is present in many fruits and vegetables, but its richest source is primarily tomatoes (*Lycopersicon esculentum* Mill.), which are intended for direct consumption or processing (Banafsheh & Sirous 2016). Lycopene is the strongest antioxidant, shows the strongest singlet oxygen quenching capacity compared to α-tocopherol and β-carotene. This substance performs other functions in the primary environment (fruit), protecting them against oxidative stress, the harmful effects of light and other factors. Due to its hydrophobicity and the consumption of oils and fats, the bioavailability of lycopene is high after consuming lipophilic foods. The health-promoting properties of lycopene have been confirmed in clinical trials, although the mechanisms of action of this compound are still not fully understood (Bacanli *et al.,* 2017).

Many of the aforementioned secondary metabolites exhibit antioxidant activity, protecting against oxidation. Aerobic organisms continually produce free radicals. Their source is molecular oxygen and are then called reactive oxygen species (ROS). Free radicals, asperoxyl radical, alkoxyl radical, hydrogen peroxide, superoxide anion, hydrogen peroxide, hydroxyl radical, or organic hydroperoxide are highly unstable, containing one or more unpaired electrons on their outermost orbitals, making them quite reactive. In addition, free radicals arise from exposure to biotic and abiotic factors. Lifestyle, often characterized by low physical activity, consumption of highly processed foods and exposure to various chemicals, plays a key role in causing oxidative stress (Sharifi-Rad *et al.,* 2021a; Pizzino *et al.,* 2017).

Free radicals are essential in the human body, in low concentrations, for the synthesis of certain cell structures and the host's defense against pathogens. When pathogenic microorganisms are present, free radicals synthesized and present in phagocytes maybe released to eliminate them (Sharifi-Rad*et al.,* 2021a; Pizzino *et al.,* 2017). The occurrence of ROS in small or moderate amounts, affects the regulation of processes related to the maintenance of homeostasis and the functioning of various vital activities. For normal body functions, a balance between free radicals and antioxidants is needed (Bhattacharyya *et al.,* 2014). Free radicals can potentially damage biologically important molecules: proteins, fats and carbohydrates. Diseases such as diabetes, cancer, cardiovascular and neurodegenerative diseases can be caused by an excess of free radicals in the body (Burnaz *et al.,* 2017; Aminjan *et al.,* 2019). Free radicals can also damage lipids, proteins, DNA and cell membranes (Ayala*et al.,* 2016). ROS, in turn, can damage DNA due to the oxidation of deoxyribose, breaking nucleotide strands, destroying nucleotides, modernizing the bases, and cross-linking DNA with proteins (Liang *et al.,* 2020).

Natural compounds can improve immune function and reduce oxidative stress (Ricordi *et al.,* 2015). The role of free radical scavengers is played by biologically active substances contained in herbs and spice plants. Their action is to donate a hydrogen atom and thus block the action of free radicals. Antioxidant compounds have a low activation energy, so the formed free radicals are stabilized by electron delocalization. This means that they do not react easily and create additional free radicals (Tan *et al.,* 2018). Most antioxidant substances found in plants are phenols, which function as chain-breaking antioxidants because their -OH group scavenges reactive radicals. They are found primarily in leaves, seeds, stems,

fruits, bark, flower tissues and other stringy or woody parts of plants. Extracts of rosehip, cinnamon, oregano, black pepper, nutmeg, and black pepper have the ability to scavenge free radicals and to chelate Fe^{2+} and Cu^{2+}(Pizzino *et al.,* 2017; Tan *et al.,* 2018). The excess of free radicals in the body is known as oxidative stress. In the absence of neutralizing antioxidants, inflammation of the joints, blood vessels, glomerulonephritis, respiratory disease in adults, heart disease, strokes, anemia or neurological disorders occurs (Pizzino *et al.,* 2017, Shahidi and Ambigaipalan 2015; Mao *et al.,* 2017; Sen *et al.,* 2020). A cell imbalance between antioxidants and pro-oxidants is called oxidative stress. When the body's defense system is too weak to neutralize free radicals, exogenous antioxidants are essential (Pizzino *et al.,* 2017). The natural antioxidants can be found in natural food (Sokamte *et al.,* 2019). Antioxidants play a large role in counteracting or slowing the progression of diseases caused by oxidative stress (Pizzino *et al.,* 2017; Sen *et al.,* 2020). The availability of bioactive ingredients includes activities such as absorption, distribution, metabolism, excretion, and biochemical and physiological effects. The administration of bioactive ingredients through food products takes place orally. However, the absorption of these components into the systemic circulation is hampered by, for example, the acidic environment in the stomach, the metabolism of liver enzymes or closely related enterocytes (Jafari *et al.,* 2017).

To obtain bioactive compounds from vegetables and medicinal plants, classical techniques such as Soxhlet extraction, maceration or hydrodistillation can be used (Azmir *et al.,* 2013). These techniques are some disadvantages, such as: limited recovery, use of more extraction solvents, longer extraction times and other (Alara *et al.,* 2021). Recently many new methods of obtaining plant bioactive compounds have been developed, as: include supercritical CO_2 extraction (SC-CO_2), microwave assisted extraction (MAE), ultrasound assisted extraction (UAE), enzymes (EAE), pressure extraction (PFE), and a mixing of these methods. Advantages of new methods, compared to conventional are smaller volume of solvent, higher yield, better repeatability of the process, lower number of toxic residues, and shorter extraction time (Jafari *et al.,* 2017; Alara *et al.,* 2021).

Most of the bioactive compounds in food do not sufficiently penetrate the small intestine. Hence, the developed technologies that increase the absorption of bioactive compounds. These include nanoparticles, intestinal penetration enhancers and mucolytics (McClements *et al.,* 2015; Norton *et al.,* 2015; Ruseska *et al.,* 2021). Oral nanoemulsions significantly improve the absorption of nutraceuticals, such as curcumin and alpha-tocopherol, compared to non-encapsulated forms. Moreover, the bioavailability of hydrophobic bioactive substances can be improved by using special emulsions consisting of lipid droplets dispersed in an aqueous phase. Alternatively, the active ingredients can be used in the form of natural fruits or vegetables, or consumed in emulsion systems (Varzakas *et al.,* 2016). The effects of bioactive compounds on body can be exceedingly small over a relatively abbreviated period of time. When bioactive substances consumed in the daily diet, they can contribute to significant improvements in the functioning of the human body (Biesalski *et al.,* 2009; Taheri *et al.,* 2022).

One method of preserving bioactive substances is encapsulation, which involves the encapsulation of one substance, called the core material, into another substance (a shell or bearing wall) (Vos *et al.,* 2010). Thanks to this technique, it is possible to extend the shelf life of products and protect active ingredients against degradation. You can also mask any undesirable taste or smell. The physical properties of encapsulation systems, such as shape, size, surface charge, as well as their mechanical properties, have a significant impact on the formation of encapsulated components in the human bloodstream, regardless of the technique used (Jafari*et al.,* 2017; Ruseska *et al.,* 2021).This allows for greater protection against adverse factors, including improved water solubility, improved intestinal absorption and lymphatic translocation (Varzakas *et al.,* 2016; Salehi*et al.,* 2019b).

The use of nanotechnology is an innovative approach to improving the solubility and bioavailability of bioactive ingredients contained in food (Salehi *et al.,* 2019b; Ruseska *et al.,* 2021; Recharla *et al.,* 2017). The technique of nanoencapsulation is currently the most interesting due to the benefits related to improving the stability and viability of food products. Nanoencapsulation can concern compounds such as carbohydrates, proteins and lipids. The advantages of nanoparticles, especially those based on lipids, relate to the higher encapsulation efficiency and its targeted activity. This gives good results in the work on lipid-based transporters, which can then be used in the pharmaceutical and food industries (Sharifi-Rad *et al.,* 2021b; Ruseska *et al.,* 2021; Katouzian *et al.,* 2017).

Other forms and techniques such as nanoemulsions, nanoliposomes, and polymeric mineral nanoparticles are also used. Encapsulated nanoparticles can penetrate the intestinal epithelium by paracellular route or through cells by the mechanism of transcytosis. Such uncharged components can also pass through the epithelium due to diffusion through cells, the so-called by the transcellular route (Jafari *et al.,* 2017). The development of liposomes as a more accessible system for biologically active ingredients such as phosphatidylcholine, melatonin and cholesterol has been studied using supercritical carbon dioxide (SC-CO_2) (Situ *et al.,* 2017). It turned out that melatonin liposomes were resistant to degradation in the simulated gastric environment and improved the bioavailability of melatonin through a controlled release process only in the simulated environment of the small intestine (Ruseska *et al.,* 2021).

The effectiveness of functional products and nutraceuticals in disease prevention depends on the bioactivity, bioavailability and stability of active food ingredients (Fang & Bhandari, 2010; Silva *et al.,* 2016; Jafari et al. 2017, Ruseska *et al.,* 2021). Only a small fraction of active compounds remains orally available (Silva *et al.,* 2016). Macromolecular biomolecules are now replacing traditional therapies due to their improved targeting and delivery capabilities. Protamine is currently the best candidate for a nanopharmaceutical. It is a small polycationic peptide (Ruseska *et al.,* 2021). They are based on innovative nanopharmaceutical systems that deliver drugs containing protamine as a carrier of biologically active ingredients, such as DNA or RNA. There is also intensive research on protamine-related nanotechnology, as well as the process of producing self-assembling particles, on the engineering of nanoparticles. Protamine's modifying and immunomodulating properties make it a key component of new vaccine technologies in RNA delivery systems and their application in cancer treatment (Ruseska *et al.,* 2021).

Nanotechnology has many applications. There are already medicines on the market made with this technology. Today, nanotechnology is attracting increasing interest in many countries, both from government and the commercial sector. Most classical drug delivery systems (CDDS) are characterized by a lightning-fast release of the drug after administration, which leads to more frequent administration. Therefore, there is a lot of research worldwide focusing on the development of pharmaceutical nanomedicine and its transformation into products manufactured by pharmaceutical companies (Halwani *et al.,* 2022). Plant bioactive compounds are expected to be a natural alternative in the treatment and prevention of diseases such as cancer, nervous system diseases and others. The development of new technologies, nanotechnologies and methods will be an opportunity to increase the production of drugs, pharmaceuticals, nutraceuticals and pay more attention to the bioactivity of food (Alfei *et al.,* 2020; De Araújo*et al.,* 2020; Câmara *et al.,* 2021; Halwani *et al.,* 2022).

INFLUENCE OF MEDICINAL PLANTS ON THE CENTRAL NERVOUS SYSTEM

Herbal medicine has been used, for hundreds of years. Combining powerful drugs with natural bioenhancers to boost bioavailability is becoming more popular (Saraf, 2010; Alexander *et al.,* 2012; Khan*et al.,* 2013). Piperine, quercetin, genistein, naringin, sinomenine, curcumin, and glycyrrhizin, among other herbal components, have been proven to improve pharmacokinetics, which has been successful in increasing oral absorption of nutraceuticals such as vitamins, minerals, amino acids, and some herbal compounds. This comprises the absorption process, drug metabolism, and drug target action. Herbal bioenhancers are readily available, safe, and free of adverse effects. They reduce drug toxicity, shorten treatment time, reduce drug resistance issues, and reduce treatment costs. Despite the fact that herbal bio-enhancers offer a novel approach to increasing the bioavailability of a variety of powerful medications, there are a number of herbal bioenhancers that have still to be investigated in a number of key areas. These bio-enhancers must also be indicated to improve bioavailability and bioefficacy of drugs delivered via methods other than the oral route (Alexander *et al.,* 2014). A bioenhancer is a substance that has no inherent pharmacological activity but increases the bioavailability and efficacy of a medicine when given together with it. When he blended vasaka (*Adhatoda vasica*) leaves with long pepper in 1929, Bose was the first to claim improved antiasthmatic potential. The concept of natural 'bioavailability boosters' derives from the Ayurvedic medical system's ancient wisdom. As a result, treatments are becoming more widely available, particularly to those who are financially challenged. One technique for lowering medicine dosage and, as a result, drug toxicity and cost is to increase pharmaceutical bioavailability (Atal & Bedi, 2010).

Man's use of antibiotics and other medications is expanding at an alarming rate. Depending on the antibiotic class, 20–50% of the total medications and chemicals used are unneeded. Furthermore, indiscriminate antibiotic usage develops antibiotic resistance, which leads to multiple drug resistance and makes illness control more difficult. Infected people need to take more antibiotics, this could be owing to decreased absorption in the gut membrane when taken orally, restricted uptake by the target microorganism, or efflux pump function resulting in indiscriminate outflow of antibiotics or therapeutic compounds. As a result, the majority of the medicine is squandered, with only a little portion being sent to the infection site (Khanuja *et al.,* 2003).

Bioavailability is important in medicine because plasma concentrations and, as a result, therapeutic efficacy are influenced directly by bioavailability. Bioavailability increase can lower the required dose of pharmaceuticals, making expensive drugs more affordable and reducing unpleasant side effects (Kesarwani *et al.,* 2013).

Antidepressant

Traditional medicine, which uses therapeutic plants and plant extracts, has existed alongside modern Western medicine for millennia. Sixty percent of the more than 300,000 seed plants have been used for therapeutic purposes (Jiao *et al.,* 2011), South America, Africa, and Asia, in particular (Cercato *et al.,* 2015; Olivier*et al.,* 2015; Lü *et al.,* 2015). Thousands of vegetal extracts have been tested in the treatment of a variety of ailments, including obesity (Olivier *et al.,* 2015), rheumatoid arthritis (Lü *et al.,* 2015), diabètes (Shori 2015), malaria (Memvanga *et al.,* 2015), and, not least, central nervous system problèmes (Farahani *et al.,* 2015;Sucher & Carles 2015).

Plants are an important source of a variety of secondary metabolites that are used to treat and prevent diseases. Anticonvulsant, antidepressant, antianxiety, sedative, locomotor activity, and memory enhancing properties were found in many therapeutic plants. They have also been shown to help with Parkinson's disease, Alzheimer's disease, dementia, stress, and fatigue, among other neurological diseases. Antidepressant benefits were attributed to medicinal plants via synaptic control of serotonin, noradrenaline, and dopamine, as well as influencing hypothalamic-pituitary-adrenal axis activity and antioxidant properties (Rabiei & Rabiei 2017). They have sedative and anxiolytic effects via potentiating inhibitory neurotransmission or reducing excitatory neurotransmission. Modulation of neuronal communication via specific plant metabolites binding to neurotransmitter/ neuromodulator receptors, stimulation or sedation of CNS activity, and regulation or support of the endocrine system's healthy function were among the mechanisms of action of medicinal plants used to treat psychiatric disorders (Sarris, 2007; Spinella, 2001). Considerable amount of therapeutic plant action is directed towards the central nervous system (Zhu, 1996). Both G protein-coupled receptors (GPCRs) and ion channels play important functions in the CNS (Bockaert & Pin, 1999; Waszkielewicz *et al.,* 2013). They mediate signal transduction activities caused by neurotransmitters and other molecules in the CNS, and malfunction results in inactive, overexpressed, or constitutively active molecules, which can induce ligand binding, receptor desensitization, and recycling, potentially leading to disease (Thompson *et al.,* 2008, Nazıroglu & Demirdas, 2015). Plant extracts and/or their components have been shown to have a direct effect on GPCRs and ion channels in the CNS in a number of studies, making them potential targets for drug development alongside conventional pharmacological molecules (Lundstrom, 2016; Kim, 2010). Most medicinal plants were found to have antidepressant effects by regulating serotonin, noradrenaline, and dopamine synoptically, regulating the activity of the hypothalamic-pituitary-adrenal axis, reinforcing the antioxidant defense system, and lowering inflammatory mediators. Medicinal herbs and their active chemicals have been shown to alleviate depression in a variety of ways, making them a promising new source for antidepressants (Antonaci *et al.,* 2011).

Neuroprotective

Neurodegenerative illnesses such as Alzheimer's disease, Parkinson's disease, ischemia, and traumatic injury are defined by progressive neuronal loss and dysfunction. In the development of neurodegenerative disease therapeutics, many neuro-protective medicines that modify cellular responses to noxious stimuli, such as oxidative stressors, and consequently have anti-inflammatory and antiapoptotic activity have been investigated. Medicinal plant phenolic compounds have recently gained attention as potential neuroprotective agents (Kim, 2010). Antidepressant benefits were achieved by medicinal plants via synaptic modulation of serotonin, noradrenaline, and dopamine, as well as influencing the activity of the hypothalamic-pituitary-adrenal axis and antioxidant effects (Antonaci *et al.,*2011). They act as sedatives and anxiolytics by increasing inhibitory neurotransmission and decreasing excitatory neurotransmission. Modulation of neuronal communication via specific plant metabolites binding to neurotransmitter/neuromodulator receptors, stimulation or sedation of CNS activity, and regulation or support of the endocrine system's healthy function were among the mechanisms of action of medicinal plants used to treat psychiatric disorders (Katzman, 2011; Pal & Shukla, 2003).

Anxiolytic

Anxiety and depression are multifaceted mental diseases that are among the top causes of disability globally (Antonaci *et al.,* 2011). Despite the different kinds of medications available to treat anxiety and depression, complete remission has eluded researchers (Katzman, 2011). In recent clinical cases, there has been an increase in interest in phytomedicine among health practitioners and patients (Pal & Shukla, 2003). Plant-based anxiolytic and depressive drugs are developed using an ethnopharmacological survey (careful research of folkloric application of medicinal plant), phytochemical, and pharmacological studies. Medicinal herbs have long been a rich source of biomolecules with therapeutic promise in the treatment of anxiety and depression, and they will continue to be so (Fajemiroye*et al.,* 2016).

Anti-diabetes

Diabetes mellitus is a complex metabolic disease that has wreaked havoc on people's health and quality of life. Diabetes is managed with the use of traditional drugs and a healthy lifestyle. However, they are not completely effective, and no one has ever claimed to be completely free of diabetes. Medicinal plants have long been used to treat diabetes mellitus in various traditional medical systems around the world because they are rich in biological elements and several of them are known to be helpful against diabetes. Because of the fewer adverse effects and inexpensive cost, medicinal herbs with antihyperglycemic properties are becoming more popular (Rabiei & Rabiei, 2017; Khan *et al.,* 2012).

The benefits of medicinal plants with hypoglycemic effects in the therapy of diabetes mellitus have been demonstrated in numerous research. These plants' properties may help to prevent the onset of diabetes problems and repair metabolic imbalances. The World Health Organization has stated that preventing diabetes and its complications is not just a huge challenge for the future, but also necessary if universal health is to be achieved. As a result, in recent years, a lot of effort has gone into identifying plants having anti-diabetic properties that might be consumed by humans. Furthermore, it highlights the voluntary and rational use of traditional and natural indigenous remedies in this regard (Malviya *et al.,* 2010).

Cardioprotective

Cardiovascular disorders are treated with a series of chemicals derived from a variety of plant species. A variety of bioactive chemicals found in cardioprotective plants, such as diosgenin, isoflavones, sulforaphane, carotinized, catechin, and quercetin, have been shown to improve cardioprotection, lowering the risk of heart abnormalities (Fathima & Vasudeva Murthy, 2018). Herbal antioxidants are becoming more popular as protective agents against a variety of cardiovascular disorders. Bioactive substances derived from natural sources have become increasingly important in modern medicine, reducing the risk of heart disease by preventing the generation of free radicals (Wang *et al.,* 2007).

Herbal remedies serve a key role in health care for a vast number of the world's population and are regarded as part of diverse tribes' cultural heritage. Polyphenols protect the heart by inhibiting the oxidation of low-density lipoprotein (Low density lipoprotein) (Portincasa & Calamita, 2019).

Anti-inflammatory

Inflammation is a very dynamic process that can be described as the immune system's first defensive response. A successful and well-controlled inflammatory response is a beneficial process that leads to the removal of harmful stimuli and the restoration of normal physiology, which is precisely controlled by a complex molecular cascade (Tasneem *et al.,* 2018). The inflammatory reaction has long been divided into various components, including redness, heat, discomfort, and oedema. Inflammatory injuries cause the production of a number of systemic mediators, such as cytokines and chemokines, which orchestrate cellular infiltration and, as a result, bring the inflammatory response to a halt and tissue integrity to be restored. Chronic inflammation, on the other hand, can be caused by persistent inflammatory stimuli or a malfunction of the resolution phase's systems (Maione *et al.,* 2016; Dawid-Pać 2013).

Antimicrobial Activities

Long before civilization discovered germs, it was commonly recognized that certain plants had healing capabilities and included what we now refer to as antimicrobial principles. Since antiquity, plants have been used to treat common infectious diseases, and some of these ancient treatments are still used today to treat a variety of conditions. Many researchers are interested in identifying the antimicrobial activity of plant extracts used in folk medicine, essential oils, or isolated chemicals such alkaloids, flavonoids, sesquiterpene lactones, diterpenes, triterpenes, or naphthoquinones. The usage of bearberry (*Arctostaphylos uva-ursi*) and cranberry juice (*Vaccinium macrocarpon*) to treat urinary tract infections, for example, has been described in many phytomedicine journals. Some of these compounds were separated or acquired through bio-guided isolation after the plant's antibacterial action was discovered (Belemtougri *et al.,* 2006).

Anticancer

Cancer is a highly fatal disease in which the body's cells divide uncontrollably and grow out of control. These cells then infect healthy cells, spreading the infection throughout the body. Cancer is a collection of connected diseases rather than a single disease. Cancer is thought to be the cause of the highest incidence of mortality in the world's human population (Gezici & Şekeroğlu, 2019). Every year, it affects six million people. According to the American Cancer Society, cancer affects about 0.5% each year. Cancer is caused by mutations in the molecular mechanisms of genes that control normal cell growth. Oncogenesis cannot be prevented without a proper balance of gene function. Cancers of the breast, prostate, cervix, lung, intestine or colon, and anal region, among others, will be the topic of our discussion. Our research will also look into the molecular underpinnings of cancer. Herbal medications with anticancer potential have grown in popularity, and research in this field has surpassed expectations in the previous decade. According to estimates, there are approximately 250,000 species of higher plants on the planet, with 35,000–70,000 species being utilized to cure various ailments due to the presence of secondary metabolites (Koul, 2020).

UV radiation, tobacco smoke, viral, bacterial, and parasite infections, mycotoxin contamination of foods, free radicals, and reactive oxygen species are some of the physiological and biochemical mechanisms that produce chronic diseases like cancer. Cancer is the second leading cause of death, after cardiovascular diseases. Globally, cancer deaths are anticipated to increase from 7.1 million in 2002 to

11.5 million in 2030. It was a pivotal moment in the effort to prevent cancer and find a treatment that works. Chemotherapy and radiotherapy, for example, are expensive and have a myriad of adverse effects, including nausea, alopecia, diarrhea, constipation, myelosuppression, neurological, cardiac, pulmonary, and renal damage. As a result, more selective and less toxic anticancer treatments are required than those already in use (Oran & Al-Eisawi, 1998).

Antiviral

Medicinal plants are a rich source of a variety of chemical components that can be used to generate novel chemotherapeutic medicines to combat a variety of human infections. The mechanism of antiviral activity of plant extracts or chemicals differs depending on the virus. Some plant phytochemicals inhibit viral genome formation or virus adhesion to the host cellular machinery for reproduction, while others impair viral encoding enzymes (Zhao *et al.,* 2014; Callies *et al.,* 2015; Zamani *et al.,* 2015). Antiviral chemicals are found in many plants; for example, rutin, a flavonoid glycoside found in many plants, is effective against avian influenza virus, HSV-1, HSV-2, and parainfluenza-3 virus (Zamani *et al.,* 2015; Vidal *et al.,* 2012). Many plants contain antiviral compounds, for example, rutin, a flavonoid glycoside found in a variety of plants, is effective against the avian influenza virus. HSV-1 and HSV-2 are two types of herpes simplex viruses (Omar *et al.,* 2018), and parainfluenza-3 virus (Orhan *et al.,* 2010; Yuan *et al.,* 2014).

Quercetin, a rutin aglycone found in plants, has been demonstrated to prevent the replication of a range of viruses, including the highly pathogenic influenza virus(Wu, 2016). Baicalin (the glucuronide of baicalein) was found to be effective against a variety of viruses, including enterovirus (Li *et al.,* 2015), dengue virus (Moghaddam *et al.,* 2014), respiratory syncytial virus (Pizzino *et al.,* 2017), and Newcastle disease virus were all found to be resistant to baicalin (the glucuronide of baicalein). The plant triterpenoids oleanolic acid and ursolic acid, which can decrease enterovirus 71 replication, may be effective against HCV by decreasing HCV NS5B RdRp pathogenicity (Shi *et al.,* 2016; Kong *et al.,* 2013).

Anti-thyroid

The thyroid gland, which generates and secretes thyroid hormones, is a tiny gland in the body that when it malfunctions, it disrupts energy production and causes fatigue (Aleebrahim-Dehkordy *et al.,* 2018). Hypothyroidism and hyperthyroidism can interfere with metabolism and proper tissue function (Danforth & Burger, 1984, McAninch & Bianco, 2016). Hypothyroidism and hyperthyroidism can disrupt metabolism and normal activities of the body's tissues since the roles of thyroid glands in numerous body functions have been thoroughly explained. People's willingness to utilize these substances, which are regarded to be low risk and have no side effects, is expanding (Süntar, 2020). Because thyroid hormone levels fluctuate, they have a considerable impact on human physiology and play a role in the development of a variety of illnesses. Thyroid hormone abnormalities have been related to an increased risk of heart disease, diabetes, depression, menstrual irregularities, and kidney disease (Vargas-Uricoechea *et al.,* 2014). The most effective compounds on these hormones are flavonoids, coumarins, alkaloids, minerals, essential oil components such as terpinene, gamma terpinene, and limonene, and antioxidant compounds that directly influence thyroid and change serum levels of thyroid hormones by inhibiting thyroid peroxidase (Zehra *et al.,* 2019). A decrease in lipoxygenase activity and an increase in catalase and dismutase activity are two more ways that plant-based compounds can affect thyroid hormone levels

(Chainy & Sahoo, 2020). It may thus be argued that developing medications for thyroid illnesses utilizing medicinal plants and their components is an innovative and efficient technique.

Hepatoprotective Agents

Oxygen radical's lipid peroxidation is one of the most common causes of cell membrane damage, which can result in a range of disorders. One of the world's most critical health problems is liver disease. Their current medical care is judged poor, despite their high frequency, morbidity, and fatality rates. There is yet to be a medicine that has shown complete success in halting disease progression. Furthermore, new drugs for the treatment of chronic liver disease are typically associated with a slew of negative side effects. As a result, medicinal plants have long been recognized as a rich source of new therapeutic drugs that could benefit in the treatment of liver illnesses, particularly those with a long history of use (Shehab *et al.,* 2020).

Natural liver cures have a lengthy track record of success. So far, hundreds of plants have been investigated to see if they may be utilized to treat a range of liver disorders. Natural therapies, such as plant extracts, may be useful in the treatment of a swollen liver. According to trustworthy scientific knowledge gathered via medicinal plant research, plants like *Silybum marianum*, *Glycyrrhiza glabra*, *Phyllanthus species* (amarus, niruri, embolic), and *Picrorhiza kurroa* have been widely and largely successfully utilized for the treatment of liver issues (Rouf *et al.,* 2021).

CLINICAL TESTS

Herbal medicines can have the status of a medicinal product if it is well documented by chemical composition studies, in vivo, in vitro and clinical trials. The list of such species evaluated in vivo, in vitro and clinically is not long, but in the second group there are traditional medicinal products, well-researched, with a long enough tradition confirming the effectiveness of their use. The list of such species tested in vivo, in vitro and clinically is not long, but in the second group there are traditional medicinal products, well-researched, with a long enough tradition confirming the effectiveness of their use (Nandagopal*et al.,* 2011, Hussain *et al.,* 2017). Medicinal plants are now widely acknowledged as having enormous promise for the development of clinically effective medications. Plant materials in powder, syrup, or lotion form have traditionally been utilized by medical practitioners without identification, measurement, or dose restriction (Nandagopal*et al.,* 2011). Antimicrobial, anticancer, antidiabetic, analgesic, and anti-inflammatory actions of medicinal plants are linked to the presence of several bioactive chemicals such as phenolic acids, flavonoids, and terpenoid. *In vitro* research demonstrated that medicinal plants inhibit various enzymes involved in inflammatory processes, whereas in vivo studies revealed anti-inflammatory and analgesic properties. Various bioactive compounds having anti-inflammatory and analgesic properties in vitro and in vivo, as well as various modes of action, have been discovered. In clinical studies, unique secondary metabolites from some plants and their bioactive components were discovered to have considerable anti-inflammatory properties (Bouyahya *et al.,* 2022). Therefore, this section highlights the new insight into the medicinal use, chemical composition, pharmacological properties and safety profile of medicinal plants to guide future work to accurately assess their clinical value.

Saddiq et al. (2022) investigated the phytochemical composition as well as the antimicrobial and antigenotoxic properties of ethanol extract from *Asclepias procera*. Thirty-one compounds have been

identified. The main ingredients turned out to be alpha-amyrin (39.4%), lupeol acetate (17.9%), phytol (13.3%), hexadecenoic acid (5.6%), stigmasterol (3.2%), linolenic acid (3.0%) and gombasterol A (2.1%). This species has antimicrobial activity and minimal inhibitory concentration (MIC) against six pathogenic microbial strains. *A. procera* extracts were found to be significantly active against *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Escherichia coli*, with inhibition zones of 18.7, 21.3 and 23.9 mm, respectively. The plant extract was found to be a moderate inhibitor against *Bacillus subtilis* with MIC values ranging from 0.60-1.50 $mgml^{-1}$. *Actinomycetes* was considered a moderate inhibitor against *S. aureus* (MIC 86 $\mu g\ ml^{-1}$) and a strong inhibitor of CALT_two strains, against *Candida albicans* (MIC 35 $\mu g\ ml^{-1}$). Effect of *A. procera* extract on genotoxicity, somatic cells and DNA fragmentation tests assessing chromosomal abnormalities in mice. Oral pretreatment of *A. procera* (50,100 and 200 mg/kg body weight) for 1,7 and 14 days in animals treated with cyclophosphamide has been shown to significantly reduce the number of chromosomes abnormalities as well as DNA fragmentation in a dose-dependent manner. These results suggest that *A. procera* extract has antimicrobial activity and exerts an antigenotoxic effect on CP-induced genotoxicity. Moreover, *Actinomycetes* inhabiting its rhizosphere have potential antimicrobial activity (Bouyahya *et al.,* 2022; Saddiq *et al.,* 2022).

Melissa officinalis, as a known medicinal plant, has also been experimented in clinical settings, showing interesting properties in the fight against various human diseases such as anxiety, sleep problems, palpitations, hypertension, depression, dementia, infantile colic, bruxism, metabolic problems, disease Alzheimer's and sexual dysfunction. Although the reported events are rare and the plant can be considered safe, *M. officinalis* can have adverse effects. The authors analyzed the properties of this herb, with particular emphasis on this important drug in human studies (Sharifi-Rad, 2021e).

The effectiveness of *M. officinalis* in alleviating sex drive disorders in women was proved by Verma et al. (2015). Ninety women with this condition were treated for four weeks with a placebo and an aqueous extract of *Melissa officinalis* at a dose of two 500 mg capsules daily. The results of this study demonstrated that *M. officinalis* extract improved arousal, hydration, orgasm, satisfaction, and discomfort in female sexual desire problems when compared to placebo (Bouyahya *et al.,* 2022).

Other authors have used a combination of *M. officinalis* and *Nepeta menthoid*es in sleep disorders (Kong *et al.,* 2013). Over one hundred patients participated in the studies, but only eighty were selected after screening. Patients were treated with 1000 mg of *M. officinalis* and 400 mg of N menthoides or a placebo for four weeks. The combination of both herbal extracts has been shown to be highly active against insomnia (Kong *et al.,* 2013; Aleebrahim-Dehkordy *et al.,* 2018).

Many more examples of clinical trials of herbal medicines and confirmation of their effectiveness can be found in the literature. The easiest way to deny different therapies is that they are not EBM (Evidence-Based Medicine). Many scientific publications (Shehab *et al.,* 2015; Sharifi-Rad 2021e; Rouf *et al.,* 2021; Bouyahya *et al.,* 2022; Saddiq *et al.,* 2022) also point to the imperfections of the methods of clinical trials, evaluation of the results of clinical trials, the presentation of results not in absolute values, which do not result in great benefits, but relative ones. There is still too little clinical research on herbs that cannot be patented and reap the benefits. Clinical trials require sponsors to reimburse their costs, and research on medicinal plants does not guarantee this.

HERBAL TEAS ARE POPULAR IN THE WORLD

Herbal Tea Popularity in the World

Tea is the second worldwide beverage consumed after water and by cause of combination factors are believed to play a key role such as energizing as well as refreshing taste, pleasant aroma and potential positive health effect (Sari & Velioglu, 2011). Worldwide Tea is far more popular than coffee, but the distinct geographic patterns, typically one predominates should be concerned. The world has the aspect of being separated into the second poles: people who love coffee versus the people who love tea. Herbal teas have been consumed since antiquity across ancient civilizations, from China to the Mediterranean and continue to be a popular beverage today (Erol *et al.,* 2009).

According to studies and investigations there are more tea drinkers in the world than coffee. For thousands of years people have used availed herbs considering their natural medicinal properties. Floral herbs contended with tea has given rise to what is nowadays known as wellness teas. Some well-known by safety concerns of the immunity boosting herbs which will not enhance their immunity in fact but improve their guts as well are: garlic, Ginger, Moringa, black cumin seed, Turmeric, cinnamon, Astragalus, Chamomile, sage and liquor ice. Include them in the diet of the elderly mostly in the form for tea/ Herbal tea or by adding them in their food (Arshad *et al.,* 2020).

Many herbal drinks, known as teas, have gained popularity among safe food lovers and are consumed all over the world. Some of them achieved greater demand than others, depending on their topography, regardless of the age of globalization, traditional restrictions have been gradually removed and such products, although from different areas, are now widely available as international health products (Chandrasekara & Shahidi, 2018). In 2016, the world's most tea-loving nations were: Turkey, Ireland, the United Kingdom, Iran, Russia, Morocco, New Zealand, Egypt, Poland and Japan (Meza-Valle *et al.,* 2021).

Today, many of the spices and herbs are used, as medicinal plants. The reported, spices and herbs to have positive effects in the treatment of some complex diseases. For example, the cancer cell growth and cytotoxicity are inhibited, by using some medicinal plants such as *Myristica fragrans, Garcinia gummigutta, Gymnema silvestre, Picrorhiza kurroa, Linum usitatisimum* and the clinical trials have found this compound non-toxic to human cell (Ziarati *et al.,* 2021; Shori, 2015).

Recent studies have assessed the effectiveness of plant inhibitors such as α-amylase or α-glucosidase in terms of their antidiabetic and antioxidant properties (Şanlier & Gencer, 2020). Some of the herbal spices, such as cinnamon, ginger, turmeric, fenugreek, and black cumin, are useful and effective in treating diabetes (Janssen *et al.,* 2021).

Herbal Teas Popularity as a Supportive Role to Play during the COVID-19 Pandemic

Some studies around the world proved that switch individual consumer approach and recognize the impact of unconnected details related to the COVID-19 pandemic has led to changes in individual food dietary. Nowadays people are much concerned about the kind of food they eat as such the demand for healthy food and beverages is exceedingly high. Nowadays people are much concerned about the kind of food they eat, as such the demand for healthy food and beverages is extremely high. Different varieties of COVID-19 might have affected all lifestyle and eating habits changes of people around the world. Surprisingly in some countries by low disease risks, people were exposed to common assertion about

the risks of COVID-19, which lead to some proceeding in their diets and styles. Such people may change their diets due to cope with drinking healthier beverages. Based on clinical features, consuming herbs have not been limited in Covid-19 and pandemic periods, and traditionally have been used all around the world. The approach of many people has turned to natural traditional medicine. Herbal beverages that are famous as herbal teas already being used as main part of the soul food likewise in many countries where traditional medicines are conventional and consider as folk medicine, also in many countries by diversity approaches on its antimutagenic, anticancer, antioxidant, anti-inflammatory, and antimicrobial effects. Different varieties of COVID-19 might have affected all lifestyle and eating habits changes of people around the world. Remarkably in regions and countries by fairly low disease risks, people were concerned in comprehensive connections to the risks of COVID-19, which expected to have led to proceeding in their routine diets. Such people may change their diets due to cope with drinking healthier beverages (Benavides *et al.,* 2021; Kocaadam & Şanlier, 2017).

Covid-19 has been shown to attack people with a weak immune system that protects the body from infection. The immune system is built on beneficial live bacteria living in the intestines that protect the human body against various diseases (Shori, 2015). Based on clinical features, herbal consumption was not restricted during the Covid-19 and pandemic periods, for example Curcuma longa has traditionally been used in Asia by people in many countries as a medicine or supplement for its antimutagenic, anticancer, antioxidant and antioxidant properties, and anti-inflammatory and antimicrobial activity (Abdul & Marnewick, 2021). For many years, Rooibos tea has shown strong anti-inflammatory, antioxidant, antidiabetic, anti-cancer, cardiometabolic and organ protective support and redox modulating properties (Bange *et al.,* 2018).

Most herbal teas as well as beverages afford a fine source of natural bioactive compounds like flavonoids, alkaloids, carotenoids, phenolic acids, coumarins, polyacetylenes, saponins and terpenoids, in the human diet and even many patients use spiritual/mind-body techniques/treatments as well as high doses of vitamins and herbs (most commonly polyphenols, including tea) (Monsen *et al.,* 2021). Herbal tea and beverages, consumed as assertive balanced diet, can improve the antioxidant status and many scientific investigations proved their immense potential for helping fight disease even such as cancer and infections (Ebert*et al.,* 2021; Sterling & Bowen, 2019). Additionally, due to the technological advancement and period, people have started to search for appropriate and useful herbal products.

Herbal Teas Popularity as Natural Antioxidants

One of the most principal factors which most people are concern about it in food stuffs is antioxidants. The Institute on Medicine has defined a dietary antioxidant as "a substance in foods that significantly decreases the adverse effects of reactive species (Oxygen and Nitrogen species) on normal physiological function in humans" (Shori, 2015). Antioxidants found in foods are well known for preserving the foods as well as providing important antioxidants in the body. Vegan diet with a high consumption of whole grains, vegetables, fruits, legumes, seeds, and nuts, as well as crops, and other plant- enriched nourishing foods, are widely accepted as helping to minimize the risk of oxidative stress-related disorders in addition to obesity (Lobo *et al.,* 2010; Peng *et al.,* 2014; Wright *et al.,* 2017).

Free radicals are molecules with one or more detached electrons in a nuclear orbit that are unstable, reactive and spontaneous. They can pick up or deliver an electron to other molecules making them reductants or oxidants (Bhattacharya, 2015). Free radicals are natural by-products of chemical processes such as metabolism. They can increase the risk of various diseases and accelerate the aging process

Table 2. The analysis in a variety of beverages based on the Antioxidant Food table.

Different beverages	Antioxidant Content [mmol·100 g^{-3}]
Apple Juice	0.27
Black tea, prepared	1.00
Green tea, prepared	1.50
Coffee, prepared filter and boiled	2.50
Espresso, prepared	14.2
Cocoa with milk	0.37
Cranberry juice	0.92
Grape juice	1.20
Orange juice	0.64
Pomegranate juice	2.10
Pune juice	1.00
Tomato juice	0.48
Red wine	2.50

Source: own based on Carlsen *at al.,* (2010), *mean value when n>1

(Lushchak, 2014). Exogenous sources of ROS/RNS include various environmental pollutants as well as drugs, pesticides, industrial chemicals, radiation and smoke (Yamagata, 2019).

Plant materials, animal tissues, and microbes contain chemical antioxidants. Those of plant origin can be found in fruits, vegetables, grains, legumes, oilseeds, but also in teas and some spices (Shahidi & Ambigaipalan, 2015). The most common antioxidants in plants are polyphenols, carotenoids, glutathione, tocopherols, tocotrienols, ascorbic acid and enzymes with antioxidant activity (Halliwell, 1996). Herbal drinks contain various phenolic compounds such as flavonoids, phenolic acids, coumarins, tannins, lignans and lignin's. They are well known as substances found in herbal teas or herbs intended for drinking and processed as infusions, decoctions or macerates. Fruits and vegetables are useful sources for maintaining the health of the body and prevent diseases, furthermore they can lessen oxidative stress (Shahidi & Ambigaipalan, 2015). A plant-based diet with a high proportion of fruit and vegetables minimizes the occurrence of diseases related to oxidative stress (Alfei *et al.,* 2020). Prospective health studies have

*Table 3. ORAC values of common well- known teas. Source: own based on ** USDA (2010a), *USDA (2010b)*

Teas	ORAC value (µmol TE.100 g^{-1})	
*Tea, black, ready-to-drink, plain and flavored	H – ORAC T – ORAC	313 312
* Brewed Tea, prepared with tap water	H – ORAC T – ORAC	1,128 1,129
* Brewed Green Tea	H – ORAC T – ORAC	1,253 1,254
*Ready –to-drink Green Tea	H – ORAC T – ORAC	521 521
* Ready-to-drink White Tea **Tea. *Hibiscus sabdariffa* L., prepared with tap water	H – ORAC T – ORAC H – ORAC T – ORAC	264 263 1952 1950

Table 4. Some claims for Aegle marmelos medicinal properties

Plant part	Outcome	References
Leaf extract	Antidiabetic action (in hyperglycemic rats)	Shori, (2015), Khan*et al.,* (2012); Malviya *et al.,*(2010), Şanlier & Gencer, (2020)
	Reduced cholesterol level (in diabetic patients)	Shori, (2015); Shi *et al.,*(2016); Halliwell,(1996)
	Radioprotective effects (in mice)	Kim, (2010); Shehab*et al.,* (2015)
	Antihyperlipidemic effect (in rats with isoproterenol)	Malviya *et al.,* (2010), Fathima & Vasudeva Murthy, (2018)
	induced myocardial infarction	Kim *et al.,*(2016); Aminjan *et al.,*(2019), Fathima & Vasudeva Murthy, (2018)
Root extract	Anti-inflammatory activity in animals	(Tasneem *et al.,* (2018); Maione *et al.,* (2016)
Fruit extract	Diuretic activity in rats	Awad *et al.,* (2009), Shori, (2015)
	Antidyslipidemic effects in rats	Awad *et al.,* (2009), Ignat *et al.* (2011), Sawicka *et al.* (2019)
	Reduces intraocular pressure	Suntar, (2020); Monsen *et al.,* (2021)
	Hypoglycemic activity in diabetic rats	Aleebrahim-Dehkordy *et al.,* (2018), Şanlier & Gencer (2020)
	antidiabetic action in rats	Khan *et al.,* (2012); Shori, (2015); Şanlier & Gencer (2020)
	Chemopreventive effect in Swiss albino mice	Astani *et al.* (2012); Degrou *et al.,* (2013), Sharifi-Rad*et al.,* (2021_e)
Bark extract	Antifertility activity in male Wistar rats	Lalani & Poh, (2020), Karadas *et al.,* (2016); Monsen *et al.,* (2021)

found that there is a positive correlation between antioxidant-rich diets and a reduced incidence of cancer (Godsey & Grundmann, 2016; Raskovic *et al.,* 2015). Vegetables, spices, and medicinal plants are very rich sources of antioxidants (Firuzi *et al.,* 2013). Many of the spices and herbs studied have high antioxidant content as well as high ORAC values, according to specific research. Many latest findings on plants owned the ORAC assay to reveal that the activity of antioxidant is associated to the existence of antioxidants such as flavonoids, flavones, isoflavones, coumarin lignans, catechins, isocatechins and anthocyanin (Darweesh *et al.,* 2020). Many studies have revealed that food rich consumption in antioxidants lead to less incidence of various diseases (Shahidi, 2000, Poswal *et al.,* 2019; Sawicka *et al.,* 2019). Herbal teas are popular and well known for many people as the primary sources of dietary antioxidants in many civilizations and cultures. Since the last decade, the global use of herbal teas/beverages in the form of ready-to-brew bags or plant various parts such as leaves, stems, roots, seeds, and so on has increased, leading to more studies on screening foods to determine total antioxidant capacity of everyday foods containing beverages, fruits, vegetables, spices, and herbs (Shahidi & Naczk, 2004; Carlsen *et al.,* 2010; Shahidi & Ambigaipalan, 2015). Antioxidant properties of different beverages have been reported in various categories in table 2.

Green, white and black teas, as the three best known herbal teas characterized by the highest activity and the assessment of the oxygen radical scavenging capacity (ORAC), allow to assess the degree and time needed by the extracts to inhibit the oxidizing agent's action. The values of oxygen radicals' absorbance (ORAC) (μmol TE 100 g^{-1}) of popular herbal teas are presented (Table 3). The results cannot be compared with most studies as the authors used different approaches in the extraction methods as well

as different physical conditions such as temperature, type of solvents, time and other elements, therefore taking this into account it is difficult to present a satisfactory conclusion (USDA, 2010a).

Vitamins, phenols, and carotenoids are the three most important types of natural antioxidants found in fruits and vegetables that provide protection to the human body. Carotenoids are lipophilic antioxidants, while ascorbic acid and phenols are hydrophilic antioxidants (Mercadante *et al.,* 1999; Setiawan *et al.,* 2001; Godsey & Grundmann, 2016, Hulkko *et al.,* 2022). The guava fruit (*Psidium guajava* L.) is considered a very safe and valuable fruit as it contains a significant amount of ascorbic acid (50-300 mg). This is three to six times more than oranges. Red flesh phytofluen, beta-carotene, beta-cryptoxanthin, g-carotene, lycopene, rubixanthin, cryptoflavin, lutein and neochrome are some of the carotenoids found in Brazilian guava (Müller, 1997; Thaipong *et al.,* 2006; Hulkko *et al.,* 2022). Similarly, Indonesian guava is also an excellent source of provitamin A (Zhao *et al.,* 2013).

Herbal teas are easy to prepare, moderate in action, and, in most circumstances, have negligible adverse effects. They are also inexpensive and abundant in resources and have been utilized for health care and illness prevention in many countries for thousands of years (Zhao *et al.,* 2014; Al Sulaibi *et al.,* 2020). The popularity of herbal medicine has been growingly, as one element of complementary and alternative medicine, in the worldwide. Tea infusion consists of several hundred compounds, alcohols, acids, polyphenols, and also caffeine. Tea ingredients have many health-promoting properties, incl. they prevent blood clots, support the activity of digestive juices and inhibit the transfer of cholesterol into the bloodstream. White tea has the highest CPA value, about six times higher than that of red tea, which is characterized by the weakest antioxidant properties (Al Sulaibi *et al.,* 2020). The CPA for different varieties of black and green tea is different from each other. Sri Lanka and Chinese deciduous are the dominant varieties (Table 4).

The total antioxidant potential of green tea, determined by the ability to reduce iron ions (FRAP), is higher than for black and red teas (Christensen, 2020). Green tea's CPA is typically higher than that of Black and Oolong teas. It has been proved, however, that the flavonoids contained in black tea are as effective antioxidants as the catechins contained in green tea (Chandrasekara *et al.,* 2018; Benarfa *et al.,* 2020).

Herbal Teas as a Good Sources of Natural Bioactive Compounds

There is now a growing interest in non-nutritional bioactive chemicals for food and drink as "life-span nutrients" for the prevention of non-communicable disease. Herbal drinks can improve your overall health and antioxidant status, when consumed as part of a well-balanced diet. Teas and herbal drinks are rich in the following functional groups and compounds such as alkaloids, flavonoids, carotenoids, coumarins, polyacetylenes, saponins and terpenoids. Antibacterial, antiviral, anti-inflammatory, antioxidant, antiallergic, anticoagulant, anti-mutagenic, anti-carcinogenic, anti-aging and vasodilating effects are just some of the biological effects of using natural bioactive substances. Some herbal drinks, depending on their geographic origin, are more popular around the world than others. Ethnic barriers are gradually being removed and such raw materials, albeit from different areas, are now widely available as international pro-health products (Chandrasekara *et al.,* 2018; Takshak, 2018; Embuscado, 2019; Salehi *et al.,* 2019b; Câmara *et al.,* 2021; Sharifi-Rad *et al.,* 2021a). Herbal drinks, herbal teas, are considered a natural part of the nutritional culture not only in countries where traditional medicines are widely used, but also as a medicine or supplement in many countries due to their antimutagenic, anticancer, antioxidant, antioxidant properties. Tea is the second most popular drink in the world after water, and many factors are believed

to play a key role: including its invigorating and refreshing flavor, pleasant aroma, and potential health benefits (Shori, 2015; Benavides *et al.,* 2021). Herbal tea and beverages, consumed as assertive balanced diet, can improve the antioxidant status and many scientific investigations proved their immense potential for helping fight disease even such as cancer and infections.

Many studies regarding prevention or treatment of cancers emphasized on the positive role of drinking herbal teas. Even in Medical Geology studies it has been proved that consuming herbal tea caused decreasing Arsenic concentration in blood of all people in young and older studied age sub-grouped and have significantly essential role in preventing or treatment of breast cancer (Kocaadam & Şanlier, 2017; Bange *et al.,* 2018).

Nutritional Medical Aspects of Herbal Bioactive Compounds

Since ancient times, people have been aware of the health benefits of certain herbs and medicinal plants. In recent decades, however, research into medicinal plants and cultivars as sources of bioactive chemicals has gained in popularity. Many bioactive compounds provide health benefits, especially herbs rich in bioactive compounds. Recently, many studies have been carried out on the positive effects of natural bioactive nutrients on food intake and human health. Bioactive compounds have health-promoting properties for the human body. They are evaluated for use in the prevention and treatment of a variety of diseases, including cancer, viral and bacterial infections, heart disease, chronic disease, non-communicable disease, and more. These natural bioactive chemicals have a wide range of biological and pharmacological activities, including primarily antioxidant, antibacterial, antiviral, anti-inflammatory, anti-thrombotic and vasodilating, anti-mutagenic, anti-cancer and anti-aging activities. Antioxidant compounds are widely distributed in herbs and spices, which are important sources of natural nutritional antioxidants (Takshak 2018; Sen *et al.,* 2020; Câmara *et al.,* 2021). Natural sources from various plant parts such as leaves, stems, aerial parts, roots, fruits, seeds, and flowers are used to make herbal goods and supplements. Natural bioactive chemicals are abundant in herbal products. Bioactive substances found in medicinal plants include alkaloids, carotenoids, phenolics, flavonoids, anthraquinones, coumarins, polyacetylenes, saponins, terpenoids, and many others, as well as the products derived from them (Azmir *et al.,* 2013; Jafari *et al.,* 2017).

The creation and development of nutritional medicinal herbal products or nutraceuticals with health advantages is a hot topic today, and the food and pharmaceutical companies see it as a lucrative possibility. This product launch, however, should be backed up by strong scientific evidence of the health advantages associated with the use of bioactive products and supplements. The term "Nutraceutical" was coined by combining the words "nutrition" and "pharmaceutics." It is used to describe items made from herbal extracts or dietary supplements that are utilized for more than just nutrition (Biesalski *et al.,* 2009, Shahidi, 2000; Varzakas *et al.,* 2016).

Nutraceuticals have received a lot of attention recently due to their potential nutritional and therapeutic effects. The natural items that are being used as nutraceuticals and have nutritional and medicinal benefits are classified as antioxidants, probiotics, dietary fibers and polyunsaturated fatty acids and prebiotics also including many other herbal foods. Such ingredients claim to encounter some of health problems of the people such as cardiovascular diseases, osteoporosis, arthritis and cancer etc. (Shahidi, 2000). Hippocrates has said it: "Let food be your medicine and medicine be your food." His framework is quite corresponding to the concept of nutraceuticals.

THERAPEUTIC PERSPECTIVES AS A POTENTIAL ENHANCER OF THE BIOAVAILABILITY OF ACTIVE PHARMACEUTICAL INGREDIENTS

The increasing resistance of pathogenic bacteria to antimicrobial agents is pushing researchers to develop new antimicrobial agents. Considering plants as a natural alternative to overcome drug resistance in the enterprise, infectious diseases is a key research activity because the role of plants as antimicrobial biological activates has not yet been fully explored (Binello *et al.,* 2017). Therefore, due to their poor degradability and/or membrane properties, due to the lipid barrier they must pass through to have an effect. Drug compounds can be metabolically destroyed by cytochrome P450 enzymes that are localized in intestinal enterocytes and hepatocytes (Atal & Bedi, 2010; Dudhatra *et al.,* 2012). Meanwhile, intranasal, buccal and pulmonary routes of drug delivery bypass the first-pass effect, and systemic drug distribution is still dependent on the absorption of drug molecules by mucosal surfaces. Research has shown that bioenhancers (naturally produced substances that enhance drug absorption) affect the number of unchanged drugs reaching the systemic circulation by modifying membrane permeability and/or presystemic metabolism. Patients taking medications may benefit from the use of bio-enhancers because they allow systemic delivery of these poorly bioavailable drugs via alternative routes of administration (i.e., oral, intranasal) (Dudhatra *et al.,* 2012). Genistein, curcumin, glycyrrhizin, naringin, piperine, sinomenine and quercetin, are some of the herbal constituents that, improve the pharmacokinetic properties of various potent active substances. Recent scientific studies on the ability of herbal substances to increase the bioavailability of drugs have confirmed that they also increase the absorption of nutraceuticals such as amino acids, minerals, vitamins, and some herbal ingredients taken orally. The absorption process and drug metabolism and targeting are crucial for the mechanism of drug action (Kesarwani *et al.,* 2013; Chopra *et al.,* 2016).

Bioavailability enhancers, also known as absorption enhancers, are functional excipients used in formulations to assist in better absorption of pharmacologically active drugs. Piperine was the world's first bioavailability enhancer (Chopra *et al.,* 2016; Shaikh *et al.,* 2009). Piperine is an active and main component of the plant *Piper longum* L. with the effect of increasing the bioavailability (Dudhatra *et al.,* 2012). Recent studies on several classes of drugs, including anti-tuberculosis drugs, anti-tuberculosis drugs, antibiotics, anti-inflammatory, non-steroidal drugs, CVS drugs, and CNS drugs, have produced similar supportive results. Namely, it has been proven that piperine increases the bioavailability of various drugs in the range of 30% to 200% (Shaikh *et al.,* 2009). Many scientists believe that quercetin is an enhancer of the bioavailability of active pharmaceutical substances as it improves the bioavailability, blood concentration and effectiveness of various drugs, including diltiazem, digoxin and epigallocatechin gallate. It has also been found that dietary supplementation with red onion, rich in quercetin, significantly improves the absorption of epigallocatechin gallate (Chopra *et al.,* 2016).

Another compound that increases the bioavailability of drugs is niziridine. This compound has been isolated from the leaves, pods and bark of *Moringa oleifera* and has antimicrobial (Tragulpakseerojn *et al.,* 2017; Lin *et al.,* 2019), anticancer (Falowo *et al.,* 2018), anti-inflammatory, antihypertensive, spasmolytic, antifungal (Helmy *et al.,* 2017) and antioxidant effects. The action is similar to ampicillin, rifampicin, tetracycline and nalidixic acid when used against gram-positive bacteria such as *M. smegmatis* and *Bacillus subtilis* and against gram-negative bacteria such as *E. coli*. The activity of azole antifungal drugs such as clotrimazole against *Candida albicans* is increased 5-6 times. However, an increase in the antifungal activity of this substance was observed only at higher concentrations (10 g mL^{-1}) of this compound. When combined with other compounds, it also increases the intestinal membrane absorp-

tion of nutrients and vitamin B12 by acting as a bioavailability enhancer (Tragulpakseerojn *et al.,* 2017; Falowo *et al.,* 2018; Helmy *et al.,* 2017; Hasan *et al.,* 2021). The constituents extracted from the pods of *M. oleifera* are nitrile glycosides and their derivatives. They help to increase the biological activity, bioavailability, and absorption of other drugs in combination therapy (Wahab *et al.,* 2021; Hasan *et al.,* 2021).

Glycyrrhizin is a glycoside obtained from the roots and runners of licorice (*Glycyrrhiza glabra*). It is helpful in bronchitis and allergies, asthma, gastritis, peptic ulcer disease, rheumatism and sore throat. It helps detoxify drugs and is used to treat liver disease. It strengthens immunity, stimulates the adrenal glands, and has a diuretic and laxative effect. It is most commonly used in the treatment of gastric ulcer, in diseases of the lungs and intestines (Hasan *et al.,* 2021; Salehi *et al.,* 2019a). Naringin, the main flavonoid glycoside found in grapefruit, which gives the juice a bitter taste, is also a plant compound that increases pharmaceutical bioavailability. This compound exerts a variety of pharmacological effects, such as antioxidant, blood lipid-lowering, and antitumor (Batool *et al.,* 2020). Antibiotics, including rifampicin, tetracycline and ampicillin, as well as vitamins and minerals, are better absorbed when taken with a nitrile glycoside (such as niziridine) (Chopra *et al.,* 2016; Gopalakrishnan *et al.,* 2016). In a bioactivity test, the *Moringa oleifera* fraction containing niziridine significantly increases the activity of rifampicin, ampicillin and nalidixic acid, increasing activity against gram-positive and gram-negative strains by increasing drug absorption (Chopra *et al.,* 2016; Allag *et al.,* 2020). Ginger (*Zingiber officinale*), in turn, has a strong effect on the mucosa. The en compound supports absorption by regulating the work of the intestines. It also increases the bioavailability of antibiotics such as amoxicillin (90.0%), azithromycin (85.0%), cephalexin (85.0%), cefadroxil (65.0%), erythromycin (10.5%) and cloxacillin (85.0%) (Łażewska *et al.,* 2019; Allag *et al.,* 2020). Due to its therapeutic properties, the rhizomes of *Zingiber* spp. Have a long history of ethnobotanical use. The chemical constituents of rhizome essential oil, such as zingiberene, ar-curcumen, bisabolene and sesquifellandren, have been extensively validated *in vitro* and have been associated with antimicrobial activity. Gingerols are the main active ingredients in fresh rhizome, while shogaol, a dehydrated gingerol derivative, is the sharpest ingredient in dry rhizome. *Zingiber* spp. can be a real source of natural alternatives to conventional food preservatives. Such a strategy could meet growing consumer expectations (Saddiq *et al.,* 2022).

Cumin (*Carum carvi*) contains cumin oil, which is extracted from the seeds after they are dried and crushed. The main ingredients of caraway oil are carvone and limonene. Cumin oil has antiplatelet, hypoglycemic, diuretic, antibacterial, antioxidant, antifungal and antiulcer properties. It increases the bioavailability of e.g., antibiotics, antifungal, antiviral and anticancer drugs. The extract or the oil fractions were 20-110% more active and together with *Z. officinale* they are more effective (Sachan *et al.,* 2016; Thippeswamy *et al.,* 2013; Kothari *et al.,* 2020).

Allium sativum L. containing allicin shows the fungicidal activity of amphotericin B against pathogenic fungi such as C*andida albicans, Aspergillus fumigatus* and *Saccharomyces cerevisiae* yeast (Kunnumakkara *et al.,* 2018; Cieślik & Turcza 2015).

Aloe vera (*Aloe vera* L.) and *A. barbadensis* how significant effects on both vitamin C and vitamin E. The antraglycosides present in the leaves of aloe vera: aloin, anthranol, aloe emodin, anthracene, barbaloin, emodin, cinnamic acid ester, isobarbaloin, chrysophanic acid, aloic acid, essential oils and resistannol are natural substances with laxative and analgesic properties. They have potent antibacterial, fungicidal, anti-inflammatory, anticancer, antiviral and cholesterol-lowering properties. The benefits of using this plant for bacterial and viral infections, cardiovascular diseases, Alzheimer's disease, gastrointestinal diseases, asthma and musculoskeletal ailments are immense. Anthracene derivatives, also known

as emodins, occur in free or glycosidic form and are easily oxidized. They are the main active ingredient in *Aloe vera* milk and are found in trace amounts in aloe vera gel. They show antibacterial properties: *Aloe emodin* against *Staphylococcus aureus* and *Helicobacter pylori* (Mukherjee & Pal, 2013; Kaur *et al.,* 2021) and antifungal properties: ethanolic and acetate fractions against *Aspergillus niger, Cladosporium herbarum, Fusarium moniliform,* and aloin against T*richophyton mentagrophytes*. Aloenins are the most active glycosidic α-pyrone derivatives. This group includes aloenin-A, a monoglycoside isolated from *A. arborescens*, and aloenin-B (diglycoside form). They show antifungal properties against *Aspergillus niger, Cladosporium herbarum* and *Fusarium moniliforme* (Mukherjee & Pal, 2013).

Due to the low-molecular structure, stability and high content of *Aloe vera* gel, aloenin-A turns out to be a particularly good marker for the standardization of pharmaceutical preparations. Hence, its stability and availability from aloe ointments have been studied and its biotransformation after oral administration has been determined (Saddiq *et al.,* 2022). Extracts of gel and whole leaves of *Aloe vera* increase the concentration of vitamin. C in plasma and increase the absorption of vitamin C and vitamin E. *Aloe vera* gel extract is extremely effective in slowing down and increasing the absorption of ascorbate. *Aloe vera* can increase the bioavailability of both of these vitamins and can be considered a potent herbal bio-booster of the future (Mukherjee & Pal 2013; Chopra *et al.,* 2016; Saddiq *et al.,* 2022).

Saddiq et al. (2022) showed that extracts of *Asclepias procera,* a wild shrub common throughout Saudi Arabia, are significantly active against *Klebsiella pneumonia* (*K. pneumonia*) and *Escherichia coli* (*E. coli*) and S*taphylococcus aureus* (*S. aureus*), with zones inhibitions: 21.3, 23.9 and 18.7 mm, respectively. The same plant extract was also considered a moderate inhibitor against *Bacillus subtilis* (*B. subtilis*). *Actinomycetes* were also considered a moderate inhibitor against *S. aureus* and a strong inhibitor-strain CALT-2, against *Candida albicans*. The results of the studies by these authors suggest that the extract of *A. procera* also has an antimicrobial effect and exerts an antigenotoxic effect on the genotoxicity induced by CP. Its rhizosphere-inhabiting actinomycetes have potential antimicrobial activity (Chopra *et al.,* 2016; Sarvarian *et al.,* 2022).

Common nettle (*Urtica dioica* L.), a common weed in many countries of the world. It contains phenolic compounds, sterols, fatty acids, alkaloids, terpenoids, flavonoids and lignans with excellent pharmacological activities including hepatoprotective, cardioprotective, antibacterial, anthelmintic, anticancer, antiviral, nephroprotective, anti-arthritic, antidiabetic, anti-endometrioid, antioxidant, anti-inflammatory, antiviral and anti-aging (Taheri *et al.,* 2022). In turn, in West Asia, oleaster fruits (*Elaeagnus angustifolia* L.), which are processed in the form of a dried powder, are sprinkled with fruit juices, e.g., from orange fruit (*Citrus sinensis* L.). Changes in the physicochemical activity, free radical activity, total phenolic compounds and the sensory properties of orange juice fortified with various oleaster extracts are known and appreciated. Aqueous oleaster extracts at a concentration of 20 and 25% show significant physicochemical differences in the blend of orange juice, both in the activity of free radicals and phenolic compounds.

Currently, polymeric biomaterials in combination with natural extracts are being studied as regenerative matrices or scaffolds in the field of tissue engineering. Processed hydrogels such as *Aloe vera* can be prepared in advance and enriched with conditioning ingredients (Meza-Valle *et al.,* 2021). It is suggested to reconsider the use of sterilization and stabilization methods that can significantly extend the life of the product and reduce its cost.

Controlled Drug Delivery Systems

The traditional approach of administering drugs is most often based on oral ingestion of the drug in an appropriate dose in order to obtain the desired effect in the affected area or in the painful area. Since it is difficult to plan the distribution of the drug in the body, the drug also reaches other places "by the way". The effect of this is the occurrence of side effects and the need to increase the concentration of the drug to be sure that it will have the expected effect. In addition, there are also problems with the kinetics of drug release. Again, in the traditional approach, at the beginning the drug (drug substance) is released very quickly in high concentration, after which the dosage of the drug substance is almost sinusoidal in nature (Halwani *et al.,* 2022).

It is interesting to be able to precisely deliver a drug (drug substance) as well as to precisely control its release. The use of various carriers for medicinal substances, such as hydrogels and "intelligent polymers", began to be explored in the 1960s, but significant development of research in this direction took place in the early 1980s. 38 years ago, the first drug released in Europe from biodegradable polymer microparticles was introduced in Europe. This allows for the gradual release of the active substance due to the progressive degradation of PLGA microcapsules (a copolymer of lactic and glycolic acid) (Aleksander *et al.,* 2014, Halwani *et al.,* 2022, Meza-Valle *et al.,* 2021).

Micelle and Liposomes

Controlled drug delivery systems (DDS) are both solutions designed to provide "programmed" drug release over time, as well as systems aimed at delivering a drug to a specific place in the body. Research on DDS is carried out in terms of the mechanisms of the release of active substances (e.g., by diffusion, ion exchange or osmosis), but also in terms of the kinetics of the release of these substances, materials used as carriers, delivery routes and drugs, including herbal drugs that can be used in therapy (Nakielski, 2015; Jeznach, 2017).

Micelles, liposomes, and dendrimers are the names of structures used as drug carriers in DDS therapy. They are formed under the influence of the phenomenon of self-organization of polymer macromolecules. In the case of micelles, such self-assembly leads to the formation of a core consisting of a shell and hydrophilic fragments. This structure in a drug solution causes the drug molecules to be "trapped" in the micelle core.

There are many methods for the controlled release of a drug (drug substance) from a carrier, so the polymer structure can be easily selected to obtain the correct concentration of the active substance at a given time. Another way is to use special linkers between the polymer and the drug substance, which will then degrade under certain specific conditions (e.g., lowered pH, presence of digestive enzymes, etc.). Yet another method of controlled drug release is the use of so-called "intelligent polymers" that change the structure of the carrier under the influence of pH, temperature, magnetic field, ultrasound, which allows the release of the drug (Jeznach, 2017; Halwani, *et al.,* 2022).

Transportation of the Drug

Drug delivery to the target site can be active and passive. For active transport, it is necessary to use molecules such as, for example, antibodies or proteins. They are attached to the drug carrier and allow it to be recognized at the target site. Passive transport, on the other hand, is used especially in the treatment

of cancer. Neoplastic tissue has a much greater vascular permeability compared to healthy tissues. On the other hand, in the case of ordinary, low-molecular-weight drugs, their absorption takes place in both diseased and healthy tissues. Thus, the use of macromolecular, polymeric drug carriers allows for its penetration only to places with higher vascular permeability, e.g., to cancerous tumors (Jeznach, 2017).

A novel approach is the use of nanoparticles as drug carriers. For example, magnetic iron oxide nanoparticles. In this case, the active substances attached to the drug carrier can be delivered, e.g., to the region of the tumor tissue, by means of an externally applied magnetic field. Controlled drug delivery is an issue of great interest to scientists and society as a whole. Hence, one should have the hope that research in this aspect will continue to be undertaken, and better and better therapies will have a chance to find their way from scientific laboratories to the pharmaceutical market (Jeznach, 2017).

CONCLUSION

Maintaining bioactivity is a priority for bioengineering worldwide and can be achieved by sourcing raw materials from crops, including medicinal and spice plants. Naturally occurring bioactive molecules with beneficial potential can be obtained from cultivated plants, with particular emphasis on medicinal and spice plants. However, more research is needed to determine the therapeutic and nutraceutical properties of these raw materials. Future research should focus on the nutraceutical properties of plant materials, mainly herbal ones, and the influence of various biotic and abiotic factors on the nutritional, energy and pharmaceutical value of these raw materials and products. Nevertheless, there is an important need for further *in vivo* and *in vitro* studies and clinical trials to better understand the related mechanisms of action in the treatment of various diseases. It is also interesting to control the kinetics of drug release, which provides patients with many health benefits. This leads to an improvement in the effectiveness of drugs (medicinal substances) and reduces side effects. In addition, the drug-controlled release systems also enable the active ingredient to be delivered precisely to the affected area. It is therefore one of the most interesting topics in modern pharmacology.

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Chapter 24
Bioavailability and Bio-Accessibility of Phytochemical Compounds

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ABSTRACT

Phytochemicals include a heterogeneous class of compounds (polyphenols, carotenoids, tocopherols, phytosterols, and organosulfur compounds) with different chemical structures (hydrophilic or lipophilic), distribution in nature (specific or ubiquitous), range of concentrations both in foods and in the human body, possible site of action, effectiveness against oxidative species, specificity, and biological action. Factors such as food source, chemical interactions, other biomolecules present in the food, restricted release of compounds from plant matrix, the solubility in gastrointestinal fluid, the permeability across intestinal epithelial cells, enzymatic and chemical reactions occurring within the gastrointestinal tract, drastically affect the bioavailability of these bioactive compounds. The chapter will present the essential aspects of bioavailability and bio accessibility of phytochemicals, factors limiting the oral bioavailability, as well as the new delivery approaches that have potential and can be explored to enhance the bioavailability of phytochemicals.

INTRODUCTION

Human beings are using plant-derived materials as a source for treating many diseases. A lot of processed foods as well as naturally-occurring compounds are found to have positive effect on the health of human beings. These compounds are called as nutraceuticals and the examples include carotenoids, vitamins,

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polyunsaturated fatty acids, flavonoids, peptides, proteins, curcuminoids, minerals, oligosaccharides, and dietary fibers (Espin *et al.,* 2007; Wildman & Kelley, 2007). For assessing the chemotherapeutic and chemo-preventive efficiency of these plant-based materials, they are being tested in various systems. The definition of bioavailability in the human beings states it as a substance that reaches the circulatory system after ingestion of the food material which is then delivered into specific tissues to ensure the biological availability for imparting health benefits. The potential advantages of many nutraceuticals are not very well known as they have low or variable oral bioavailability (Patel & Velikov, 2011; Fernandez-Garcia *et al.,* 2012; Rein *et al.,* 2013). The reason behind the nutraceutical's poor bioavailability is a lot of physiological and physicochemical processes such as decreased solubility in gastric juices (Porter *et al.,* 2007; Pouton & Porter, 2008), controlled release from the food matrix (Moelants *et al.,* 2012), less permeability through the epithelial cells or mucus membrane (Fleisher *et al.,* 1999; Martinez & Amidon 2002; Actis-Goretta *et al.,* 2013), development of insoluble components with other materials in the gastrointestinal tract (Rimbach *et al.,* 2008), and molecular alterations in the GIT (Hurst *et al.,* 2007; D'Ambrosio *et al.,* 2011; Fernandez-Garcia *et al.,* 2012).

Knowing these problems associated with bioavailability of different food materials could be helpful in finding different tactics to surpass its shortcomings. The major part for improving the bio-efficacy is the improvement of bioavailability of biologically active food materials. For this, the molecules are chemically or technologically modified to enhancing their solubility at the absorption site. Many research studies have also been conducted on knowing the possibility of enhancing the oral bioavailability by utilizing certain biologically active mediators like nano emulsions, microemulsions, emulsions, biopolymer nanoparticles, solid lipid nanoparticles, microgels, etc. as delivery approaches (Luo *et al.,* 2014; Yang *et al.,* 2015, Souza-Simões de *et al.,* 2017; Jain *et al.,* 2018; Silva *et al.,* 2019). This chapter, thus, aims to give a thorough review on some chief factors that have an influence on the nutraceutical's bioavailability. This chapter also put emphasis on various characteristics of plant-derived bioactive components such as digestibility and bio accessibility. Some of the new delivery approaches that have the potential to enhance bioavailability of phytochemicals are also discussed.

PHYTOCHEMICAL COMPOUNDS AND THEIR BIOLOGICAL ACTIVITY

Phytochemicals are widely known to promote health, maintain, and repair the cells, tissues as well as the entire human body. Phytochemicals are plant-derived chemical compounds that demonstrate specific health benefits even though they are not basic nutritional component (such as carbohydrate, lipids, protein, vitamins, or minerals), medicines, or toxicological compounds. The health of the human being is frequently being related with certain phytochemicals such as carotenoids, phenolics, organic acids, vitamins, curcuminoids, flavonoids and many other biologically active substances like oligosaccharides, sterols, saponins, dietary fibers, and peptides (McClements *et al.,* 2009).

The antioxidative nature of phenolic compounds makes them an interesting material for research during the last ten years. The free radical scavenging action of phenolic compounds helps in preventing many chronic diseases as well as the ones related to oxidative stress such as CVD, cancer, and some neurodegenerative diseases. Bioactivity of a compound is its ability to demonstrate a biological effect. A compound is said to be bioactive only when its absorption takes place by the epithelial cells of the intestine and then gets distributed to different tissues and organs to get involved in various biochemical pathways, thereby generating a positive health effect (physiological response). The authentication of the

physiological parameters of a biologically active component is done by evaluating the pharmacokinetic responses like liberation, absorption, distribution, metabolism, and elimination (LADME). Bioactivity gets significantly influenced by bio accessibility and bioavailability. Food materials are subjected to a wide range of biochemical, chemical and physical changes during the entire course of digestion that in turn alters the bioactivity and bioavailability of biologically active components (Hur *et al.,* 2011). For instance, some of the phenolic compounds are not assimilated in the small intestine and are passed straight to the large intestine. The microorganisms present in the large intestine then change the structure of the phenolics to form certain metabolites (Mosele *et al.,* 2015).

The bioactivities exhibited by these phytochemical compounds are well-known to have a positive effect on the health of human beings. Phenolic compounds are found to demonstrate anti-atherosclerotic, antioxidant, anti-inflammatory, anti-allergic, antithrombotic, and antibacterial properties (Del Rio *et al.,* 2013; Chen *et al.,* 2015; Dıaz-de-Cerio *et al.,* 2016; Marhuenda *et al.,* 2016). Major research has taken place in in-vitro conditions. Epidemiological research point out that consuming foods abundant in biologically active components demonstrating antioxidative properties, including phytochemicals, vitamins, and majorly phenolics, such as carotenoids and flavonoids, shows an advantageous effect on the health of human beings and can help in reducing the possibility of various diseases, viz. cardiac ailments, cancer, stroke, diabetes (Siriwardhana et al., 2013), Alzheimer's, cataract, and many other age-related functional problems (Hassimotto *et al.,* 2009). Biologically active components are able to modulate metabolic pathways and show beneficial characteristics like antioxidative nature, inhibit the activities of receptor, induction or inhibition of enzymes, and inhibition or induction of genetic expression (Carbonell-Capella *et al.,* 2014). Although, the physiological process of polyphenolic compound does not directly depend on their occurrence in the human dietary habit. The absorption of these compounds from the colon or its metabolization are indeed very poor and they quickly excrete out from the gut. Metabolites originating from the phenolics in the GIT may vary with respect to their biological activities from their original component after blood transfer to the target tissue or organ (Crozier *et al.,* 2010, Marin *et al.,* 2015).

BIOAVAILABILITY AND BIO ACCESSIBILITY

Most of the authors define oral bioavailability of nutraceuticals and nutrients as the portion of ingested amount reaching the tissues and organs and participating in the elementary metabolism or other biological routes (Parada & Aguilera, 2007). Inside the human system, the definition of bioavailability states it as a material that reaches the circulatory system after getting ingested. With the help of circulatory system, it is then delivered to target tissues or organs and becomes biologically active to impart positive health effects. The standard path for dietary phytochemicals therefore involves ingestion, digestion, and transportation through gastrointestinal epithelial layer before moving into circulatory system.

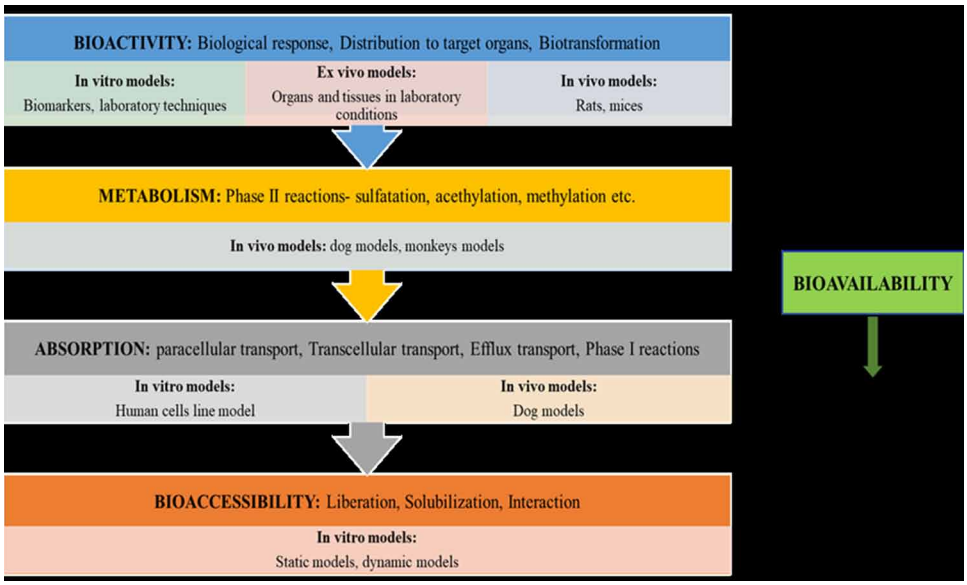
The pharmacokinetic studies aid in getting the direct bioavailability value of a component through in vivo approaches (Brake *et al.,* 2017). These researches suggest the most common bioavailability expression as the relative bioavailability expressed in terms of percentage ratio in between the AUC (area under curve) and the orally ingested drug, and also the AUC ratio with the same drug when injected intravenously, thereby giving the total absorption. The major problems occurring while studying bioavailability are complications in the biological systems. Some of them are: (a) interactions occurring between food materials and chemicals at the time of post-harvest, storage period, processing, digestion, as well as absorption that may affect the health advantages; (b) alteration in food components and human

subjects/surrogate who are not always available; and (c) the biological mechanism involved. Many food materials are not stable in gastrointestinal fluids and demonstrate poor absorption through its epithelial layer, and therefore, are considered to have low oral bioavailability (Rafiee *et al.,* 2019; Rostamabadi *et al.,* 2019). For this reason, many new studies are now focusing on knowing the possibility of enhancing the oral bioavailability by utilizing biologically active materials into a vast range of delivery approaches such as microemulsion, emulsion, nano-emulsion, biopolymer nanoparticles, solid lipid nanoparticles, microgels, etc. (Souza-Simões de *et al.,* 2017; Silva *et al.,* 2019).

The portion of ingested biocomponent that is available for absorption by the epithelial wall of the digestive system is called as Bio accessibility. The absorption of biocomponent occur only when it gets liberated from the matrix of the food or transport material and then get mixed with the associated micelles. The *in vitro* approaches determine bio accessibility very well through experimental analysis. The major factor for these determinations

The fundamental part of these establishments is the most realistic replication of the biochemical, chemical, and mechanical conditions of the four major sections of the gastro intestinal tract: buccal cavity, abdomen, small intestine, and large intestine (Alminger *et al.,* 2014). The bioavailability and bio accessibility of nutritional and biologically active compounds can be established by many ways like in vitro methods (such as Caco-2 cell, simulated gastric digestion, cell membranes, etc.), ex vivo methods (for example, digestive organs under controlled laboratory conditions), in vivo methods like animal and human researches, and in situ advanced non-thermal as well as thermal processing methods (perfusion in animal intestines) (Carbonell-Capella *et al.,* 2014). The concept of investigating models of bioavailability is demonstrated in the Figure 1. The methodology of in vitro digestion is the most commonly used approach. After that, researchers prefer the Caco-2 cell technique to study the bioactive compounds. In this technique, the cell cultures target the uptake of simulated biologically active compounds in the small bowel (Barba *et al.,* 2017). The bio accessibility of a nutraceutical could be restricted depending upon its potential to get liberated from the food component. For instance, the processing of food may cause the nutraceutical to get trapped inside the food matrix, it can also get trapped within the cells of a naturally-occurring unprocessed vegetable or fruit. The example includes a carotenoid entrapped inside the cell structure of a raw fruit and is not released completely after its ingestion in the GIT (Failla *et al.,* 2007). To enhance the bioavailability of such phytochemicals, enhancing its release from the food matrix could be a fruitful approach (Panozzo *et al.,* 2013). To achieve it, the processing conditions of food can be altered (like homogenization, shearing, and cooking), the properties of food matrix can be altered (such as structure and composition), or food habits can be changed (for e.g., time taken for mastication). The solubilization of food material into the gastric juice also affects the bio accessibility of a food material. An example of this is the low solubility of nutraceuticals into the water due to its hydrophobicity, therefore, it needs to get incorporated into a blend of micelles before absorption in the small intestine (Porter & Wasan, 2008). The bioavailability of such components can thus be enhanced by using food structures or compositions that have the ability to improve their solubility in the GIT. Further, the bioavailability of a food product is restricted in the intestine because of its interaction with other compounds present in the gastric juice. The interfering compounds could be naturally present in the gut or they may come from the consumed food material. A food material or phytochemical in this class can form a complex that is insoluble and cannot be easily absorbed within the GIT.

Figure 1. Concept of Bioavailability (Dima et al., 2020).

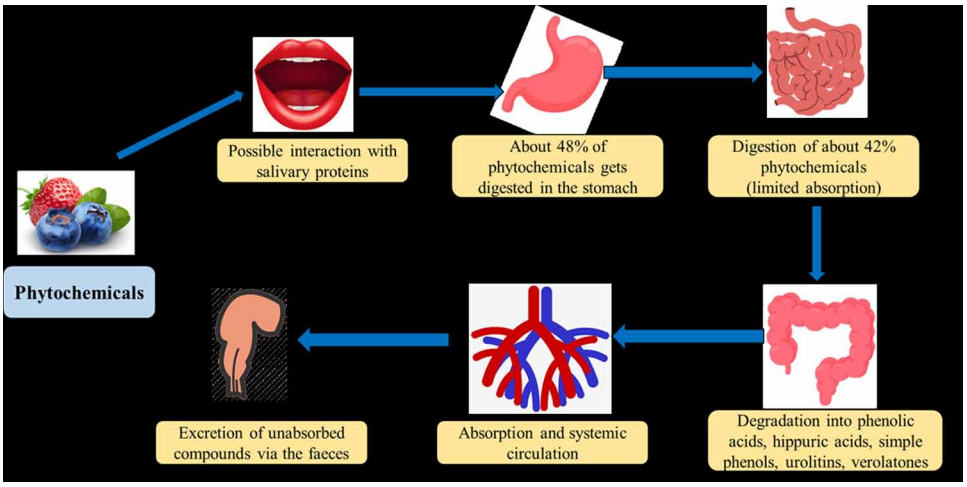


MECHANISM OF DIGESTION, ABSORPTION, AND METABOLISM OF BIOCOMPONENTS

The process of digestion in human beings is a very complicated process in which the consumed food material gets converted into nutritional components with the help of enzymatic action and mechanical alterations. The individual nutrient is then absorbed by the circulatory system and hydrolysed into the building blocks of the whole system (Figure 2). Basically, the food material turns into small fragments in the buccal cavity and stomach, while digestion as well as absorption of food occurs in the small and large intestine (Guerra *et al.,* 2012). The assimilation process starts in buccal cavity where the biologically active compounds present in the food material gets released with the help of chewing. After that, the physicochemical properties of the gastric juice and hydrolytic enzymes present in the stomach acts on the bolus, imparting certain effects on the bioavailability (Tagliazucchi *et al.,* 2012). The acidity of the stomach helps in making the phenolics stable in the GIT and also aids in the release of nutritional components from the food source (Chandrasekara & Shahidi, 2012). In the small intestine, the phenolic compounds undergo various changes under the effect of basic pH (Tagliazucchi *et al.,* 2010). Before absorption, polyphenols and proteins may react with digestive enzymes, thereby affecting the compound's bio accessibility. Bio accessibility can also be increased or decreased at the time of gastric digestion as it may interact with other components present in food such as sugars, lipids, and fibres (Ferruzzi *et al.,* 2012). Breaking the food material into small pieces during the process of mastication helps in increasing the surface area of the food, thereby increasing the effectiveness of digestion and absorption of bioactive compounds in the gut. The bioactives that are liberated from the raw material due to activity of bacterial microflora and digestive enzymes are only available (bio available) in the intestine for absorption (Saura Calixto *et al.,* 2007).

The metabolites arising from the phenolics in the GIT can have different biological activity with respect to the original material after getting transfused in the blood to reach the target tissue or organ

Figure 2. Fate of Phytochemicals in Gastrointestinal Tract (Karaś et al., 2017).



(Crozier *et al.,* 2010). The bioactives differ in their activity in every cell organelle in comparison to their functioning in the entire cell (Marin *et al.,* 2015). The cell membrane acts as a barrier, thus, affecting the bio availability of phytochemicals present intracellularly and can also decrease their geno-protective or genotoxic effect (Del Rio *et al.,* 2013). The bioavailability of phytochemicals is distinguished majorly through glycosylation, molecular weight, and esterification. A lot of phenolic aglycones demonstrates hydrophilicity and can be absorbed by diffusion through biological membranes.

One of the most important factors affecting the bioavailability of pharmaceuticals and food components is the different transport mechanisms in the intestinal lumen. The mechanisms include active transport, facilitated diffusion, and passive diffusion. The active transport mechanism works contrary to the concentration gradient and may cause both increment of components in the blood stream and reverting back of the components into the intestine. On the other hand, the mechanism of facilitated and passive diffusion works towards the concentration gradient based on the diffusion through the intestinal lining into the blood stream (Brand *et al.,* 2006). As many biologically active food components and drugs do not possess the ideal physicochemical characteristic needed for passive diffusion, therefore, transporters are required for increasing their trans-membrane movement and permeability.

FACTORS LIMITING THE BIOAVAILABILITY AND BIO ACCESSIBILITY OF PHYTOCHEMICAL COMPOUNDS

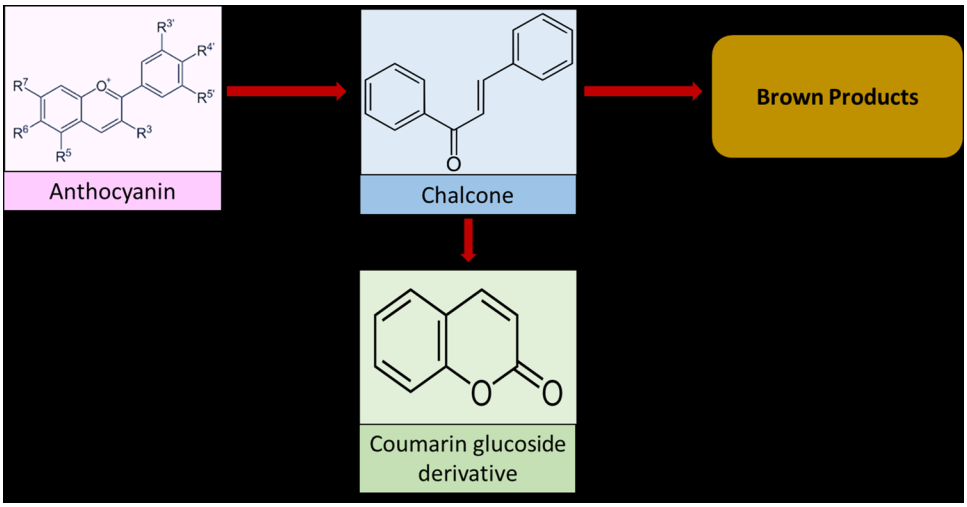
Many food processing treatments affect the bioavailability and bio accessibility of phytochemicals as it results in the breakage of the cellular structure of plant-based foods. Degradation during food processing of phytochemicals or conversion to a more active molecular structure may reduce or enhance their bio accessibility.

Degradation of Phytochemicals

Some phytochemicals are unstable and are easily degraded during food processing, thus impacting their bio accessibility and reducing the functionality for rendering health benefits. Degradation of phytochemicals is induced by food processing operations that may include high temperature, pH, light, presence of oxygen (Ioannou *et al.,* 2012), as well as the presence of other phytochemicals in food matrix (Fereidoon & Pan, 2021).

Firstly, for thermal degradation, some studies found a decrease in the antioxidant activity of phytochemicals upon heat treatments (Colle *et al.,* 2010), contributed mainly by the degradation of phytochemicals. For example, the roasting process caused a reduction of about 12% in flavonoid content, while steam heating at 0.2 MPa for 40 min induced a loss of 25% of total flavonoid content. Phytochemicals follow different mechanisms of degradation during thermal processing. For instance, the ring shaped structure of anthocyanins is opened up to form chalcone during food processing, which is broken down to form brown products (Figure 3). After forming a chalcone structure, anthocyanin is further converted into a coumarin glucoside derivative (loss of the B-ring). Carotenoids are susceptible to light, heat, iodine and oxidation through the thermal processing of food viz. cooking, heating, or drying (Sadilova *et al.,* 2007).

Figure 3. Degradation of Anthocyanin during Food Processing (Shahidi et al., 2021).



In addition, some phytochemicals show photodegradation during food processing, while some phytochemicals are synthesized. For example, presence of light develops a stress signal which increases synthesis of flavonoids in fresh foods, such as fresh-cut potatoes and onions (Rawson *et al.,* 2011). However, the anthocyanin content of fruits and vegetables may drop upon exposure to light. Moreover, pH and oxygen also cause changes during food processing. Increasing pH and oxygen concentration in beverages results in a higher rate constant of degradation of green tea (Ananingsih *et al.,* 2013). Buchner et al. (2006) reported that weak alkaline and neutral reaction conditions cause higher degradation of rutin and quercetin in the presence of oxygen.

Loss of Essential Phytochemicals Due to Chemical Reactions

Food processing causes the loss of many phytochemicals. Loss of phytochemicals is usually in two ways, one of them leads to direct production of by-products or waste. For example, some hydrophilic phytochemicals may be lost upon soaking. Some insoluble phytochemicals may be discarded as waste during juicing (Ribas-Agusti *et al.,* 2017). Meanwhile others may be degraded or oxidized in the process of chemical changes. For example, processing of food usually causes the degradation of bioactive compounds, thereby reducing their content in processed foods. Similarly, in the canning process there is a huge loss of water soluble as well as heat sensitive compounds, which causes significant reduction in amount of phenolic compounds in comparison to the original fresh fruit and vegetables (Fereidoon & Pan, 2021).

Food Processing Technologies with New Substance Formation

Food processing can produce many new substances due to chemical changes in the phytochemicals themselves or interactions with the food matrix. Some of these changes can promote the bio accessibility of phytochemicals and improve the sensory acceptability of food products, while others can compete with phytochemicals to decrease their absorption or produce substances harmful to human health. Undesirable food processing may lead to the production of compounds which adversely affects texture, flavor, or color of the products rich in phytochemicals. The undesirable compounds from food processing can be in the following forms:

Color Change

This usually happens in foods rich in polyphenols, when food is processed and exposed to oxygen, due to the action of polyphenol oxidase (PPO), the formation of several shades of colors from pink to bluish black will occur, generally termed "browning" (Nirmal et al. 2015). PPO is a copper-containing metalloprotein involved in the oxidation of phenol to quinone and causes melanosis formation. PPO activity resulted in a decreasing trend throughout the thermal treatment and followed a first-order kinetics (Wang *et al.,* 2020).

Absorption Competition Between Newly Formed Substances

The efficiency of the absorption is impacted by higher release of plant matrix components like fiber and phytosterols, competitive carotenoids and compounds possibly formed during processing (Fereidoon & Pan, 2021).

Producing Substances Harmful to Human Health

For example, after cooking, the retention of two plant-based fatty acids such as linoleic acid and a-linolenic acid will form trans fatty acids (TFA) and polymerized triacylglycerols (PTG) (Hrncirik & Zeelenberg, 2014). Many studies have demonstrated that TFA are harmful to human health and may cause a variety of chronic diseases (Otite *et al.,* 2013). However, it is feasible to standardize food formulations, process-

ing techniques and preparation processes, aiming to reduce or even prevent their formation through the use of appropriate technologies.

NEW DELIVERY APPROACHES TO ENHANCE BIOAVAILABILITY

As the realization of molecular mechanism of diseases is increasing, the list of pharmaceutical products for medicinal use is also getting increased rapidly. Although, the favorable action of a particular drug is not only kept in mind before utilizing a drug, but conditions like avoiding undesirable action of drugs on normal tissues and minimizing their side effects are also very critical points for consideration. The medicinal efficiency of any anti-cancerous drug depends both on intrinsic anti-cancerous activities as well as the bioavailability of drug at the target site. Generally, a lot of medicinal products are less soluble in aqueous medium which is directly related to decrease oral bioavailability (Bansal *et al.,* 2011; Aqil *et al.,* 2013). For developing the new therapeutic approaches, it is very much important to form an appropriate pharmaceutical formulation for delivery.

So, for treating and preventing cancer, the mode for delivering chemo preventive drugs is very crucial. The advancement of novel technologies has stimulated huge awareness for creating new drug delivery methods to improve the medicinal characteristics of intravenous medicines (Oerlemans *et al.,* 2010). To defeat the systemic toxicity and low bioavailability, many promising applications of nanosized drug carriers, such as, dendrimers, liposomes, micelles, and polymeric nanoparticles are used (Mishra *et al.,* 2010). When a comparison was made with the systemic chemotherapy, these carriers were found to have many advantages as they can enhance the delivery of anti-cancerous drugs to target sites and may also modify the pharmacokinetics of pre-existing medicines. This article puts a light on few delivery methods that are known to enhance the drug delivery at the target site or elevate the bioavailability significantly.

Nanoparticles

The researchers are now interested in developing the drug delivery methods that can use particulate delivery systems to carry large and small molecules to the target site. The size of nanoparticles ranges from 10-1000 nm and can be formed with the help of carbohydrates, proteins, lipids, and various other synthetic or natural polymers. To deliver a drug, it is either encapsulated, dissolved, entrapped, or attached to a matrix of nanoparticles. The method of preparation describes the type of obtained product, like nanospheres, nanoparticles, or nano capsules. Nowadays, a wide range of biomedical applications are being based on nanoparticle systems. During the last decade, the nanoparticle delivery systems have enormously been accepted as they have the capability to increase the medicinal index of encapsulated drugs by altering pharmacokinetics (Schluep *et al.,* 2009), delaying enzymatic degradation (Khan *et al.,* 2006), offering controlled release over a long time (Grabovac *et al.,* 2007), and reducing toxicity (Italia *et al.,* 2007; Bansal *et al.,* 2011). Nanoparticles can get adhered to the capillary wall, and hence improve the tissue uptake and oral bioavailability of insoluble medicines when administered parenterally. As nanoparticles are very small in size, they are able to leave the circulatory system to reach the site of inflammation (Davis *et al.,* 1997; Bansal *et al.,* 2011). The target site, tissue, and circulation decide the limit of nanoparticle size for going across various biological barriers (Brannon-Peppas & Blanchette, 2004). Nanoparticles can also undergo endocytosis and phagocytosis. The surface of the nanoparticles is hydrophobic in nature, due to which they can immediately get coated (opsonization) with plasma proteins

Figure 4. Advantages of Nanoparticle Delivery Systems (Paolino et al., 2021).

and engulfed by the mononuclear phagocytic system (MPS), which is found in certain organs such as bone marrow, spleen, and liver (Figure 4). But when some hydrophilic polymers, such as, PEG (polyethylene glycol) is coated on nanoparticles, it can increase the hydrophilicity, thus allowing prolonged movement in the blood along with improved uptake in non-MPS organs and deposition at inflammation sites (Davis *et al.,* 1997).

When a drug is encapsulated in nanoparticles, its pharmacokinetic characteristics and solubility gets improved. By applying this drug delivery approach, further clinical development could be achieved on those chemicals that have been held over due to the poor pharmacokinetic characteristics (Alexis *et al.,* 2008). Various researchers have used different components such as narigenin (Sulfikkarali *et al.,* 2012), curcumin (Bisht et al., 2007), and epigallocatechin gallate (Siddiqui *et al.,* 2009; Hu *et al.,* 2012). The medicines formulated by nano materials demonstrate good stability in blood, is non-toxic, non-thrombogenic, non-immunogenic, non-inflammatory, deactivates neutrophils, biodegradable, and can be applied to deliver many molecules like nucleic acids, peptides, proteins, as well as drugs (Rieux *et al.,* 2006). Much attention has been received by nanoparticles based on stimuli-responsive polymers in the field of gene and drug delivery, biosensors, as well as tissue engineering (Bae *et al.,* 2003; Xue *et*

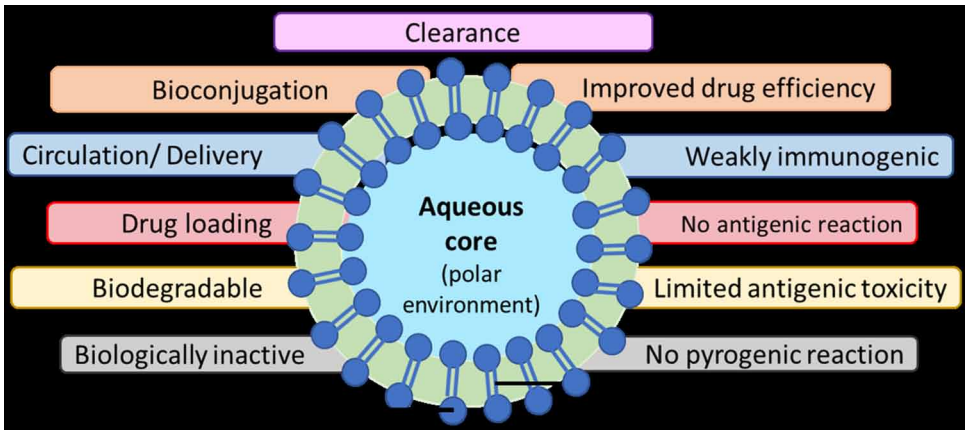
al., 2009). These types of nanoparticles undergo drastic changes in response to changing environmental conditions, like magnetic field, temperature, pH, light, or glucose concentration (Gil & Hudson, 2004; Zhao, 2009). A study was conducted on biologically responsive nanoparticles for drug delivery approach that releases their drug in reversion to variation in oxidative stress and pH (Colson & Grinstaff, 2012). These would be of substantial interest as they could provide the potential to associate drug delivery to a particular disease state or location e.g., paclitaxel delivery which is loaded on pH responsive nanoparticles. The *in-vitro* test of this approach has been done against MDA-MB-231 human breast carcinoma which showed higher toxicity when a comparison was made with paclitaxel delivery on non-responsive polycaprolactone nanoparticles (Shenoy *et al.,* 2005). Another *in-vivo* research was conducted on PAC delivery on pH-responsive nanoparticles. The results indicated higher efficiency against subcutaneous SKOV-3 tumors when a comparison was made with free PAC (Devalapally *et al.,* 2007). Almost all the researchers in this field point out the full utilization of potential nanotechnology for safety issues as the vast range of nanoparticles have very little available data on experimental toxicology. However, using nanoparticles for a long time is a potential risk factor for toxicity. Production of free radicals and ROS is a primary mechanism of nanoparticle toxicity occurring due to the reaction of foreign bodies that eventually causes inflammation, oxidative stress, as well as subsequent damage to DNA, membranes, and proteins (Maurer-Jones *et al.,* 2009). Oxidative stress induced by nanoparticles takes place at the time of dissolution of iron-based nanoparticles, which generates ROS and forms OH and OOH radicals from hydrogen peroxide (H_2O_2) through Fenton reaction (Sharifi *et al.,* 2012). Nanoparticle-induced oxidative stress occurs during the dissolution of iron-based nanoparticles, which catalyzes ROS generation and formation of OOH and OH radicals from H_2O_2 via the Fenton reaction (Sharifi *et al.,* 2012). Further, some researchers suggest that nanoparticles are not genetically benign and that they influence biological behaviors at the cellular, subcellular and protein levels (Colvin, 2004). Silica dioxide nanoparticles when given intraperitoneally at 200 mg/kg body weight are reported to show an increase in the kidney weight and creatinine levels, in *in-vivo* animal model (Chervenkov *et al.,* 2007).

Liposomes

Liposomes are spherical nano-sized artificial vesicles that can be developed from naturally-occurring cholesterol and phospholipids. It has been reported that these vesicles can be used as drug carriers and immunological adjunct. Though liposomes may have different size ranging from nanometers to micrometers, but commonly its size is in the range of 25 nm to 2.5 lm (Sharma & Sharma, 1997). The distinctive feature of liposomes resides in its ability to encapsulate a wide range of components along with their diverse structure. Liposomes are able to encapsulate a wide range of drugs having different lipophilicity or solubility. The drugs can either get trapped at the interface of bilayer or inside the aqueous core of the phospholipid bilayer. Liposomes, developed from natural lipids, as depicted in figure 5, are biologically inactive, biodegradable, produce no pyrogenic or antigenic reactions, are weakly immunogenic, and have very low intrinsic toxicity (Campbell, 1983; Aqil *et al.,* 2013). Thus, it is expected that the drugs encapsulated in liposomes can be transferred without degradation resulting in less side effects for the recipients. Liposomes are drastically being used by the industries of drugs and medicines for delivering some specific drugs, enzymes, and vaccines and for the treatment and prevention of a wide range of diseases.

The investigation on liposomes have been done and they are found helpful in delivering chemotherapeutic drugs for treating cancer, radiopharmaceuticals for diagnostic imaging, vaccines for immunological

Figure 5. Structure and Properties of Liposomes (Paolino et al., 2021).

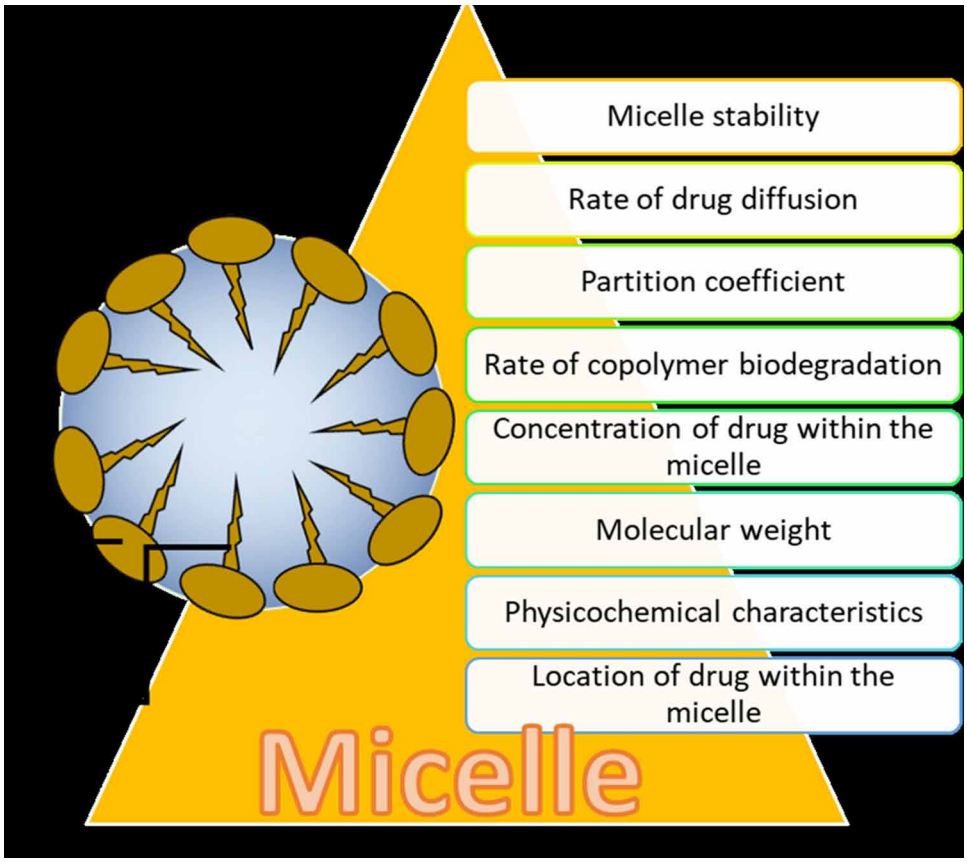


safety, and medicines based on nucleic acid for gene therapy. Various preparations have been designed and evaluated with respect to pharmacokinetic properties, relative stability, toxicity, and biodistribution. The components trapped inside the liposomes are saved from the intervention of outer modulatory influences, mainly inhibitors and enzymes (Chaize *et al.,* 2004). Furthermore, liposomes have the ability to deliver any drug, irrespective of its solubility, inside the cells by endocytosis or fusion. Liposomes have many advantages, including biocompatibility and safety, but there are certain drawbacks also, such as its instability in plasma. When liposomes are administered intravenously, certain proteins present in the serum binds to its surface (opsonin), thereby giving a signal of its presence. After the signaling of the liposomes, they quickly get captured by the MPS and eliminated from the blood stream. As a matter of interest, this particular activity has been employed for effective delivery of antimicrobial and antiparasitic drugs for treating infections that are present in the MPS (Basu & Lala, 2004). But, when the target site is beyond the MPS, the use of liposomes that are able to evade this system is required to reach longer circulation times. Previous studies suggest that prolonged circulation time of liposomes can cause significant accumulation in permeable and highly vascularized tissues, like tumors (Jain, 1998), particularly, in cases where active neoangiogenesis is involved. Tumor localization of long-circulating liposomes, such as PEG-coated (pegylated) liposomes, has a passive targeting effect that may enable substantial accumulation of encapsulated drug in interstitial fluid at the tumor site. Based on this rationale, pegylated liposomal doxorubicin delivery for cancer therapy was achieved. In this formulation, PEG coating protected the liposomes from opsonization and recognition by the reticulo-endothelial system, which resulted in prolonged circulation time, and enhanced accumulation in tumors (Gabizon & Martin, 1997). Preclinical studies suggest that stealth liposomal delivery of anthracyclines reduces the cardiotoxicity, increases the antitumor action, and enhances the overall therapeutic index (Gabizon, 2001).

Micelles

Micelles are made up of lipid molecules that forms a spherical shape in liquid medium. The size of polymeric micelles ranges from 10 to 100 nm, and they are usually very narrow. They can enhance the retention power and bioavailability of drugs, as the micellar surrounding protects the drug from inactivation. Various factors are responsible for governing the release of drugs from the micelles (Figure

Figure 6. Structure and Factors Governing the Drug Release of Micelles (Aqil et al., 2013).



6), like drug diffusion rate, micelle stability, rate of copolymer degradation, and partition coefficient (Kwon & Okano, 1996).

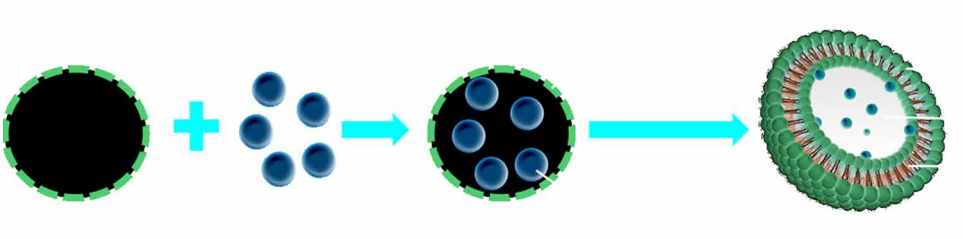
Drug release can also get affected by various factors such as the molecular weight of the drug, concentration of drug within the micelles, physicochemical properties and its position inside the micelles (Teng *et al.,* 1998). The release of drugs from different types of micelles can also be improved in the target area by many physical parameters, such as temperature, pH, light, and ultrasound. In the last decade, polymeric micelles formulated from amphiphilic block copolymers have been reported to hold a significant potential as drug delivery approach for a range of anticancer drugs due to exclusive characteristics, such as low toxicity and high solubility (Zia *et al.,* 2010). Apart from improving the solubilization of drugs, long circulation, small particle size, targeting and easy production characteristics, polymeric micelle systems can also change the drug internalization path and subcellular localization. They can also decrease the efflux of P-glycoprotein effect and, subsequently, exert a different mechanism of action from the trapped drugs (Mikhail & Allen, 2009). They also have physicochemical characteristics for tumor targeting by an improved retention effect and permeability that is a passive targeting mechanism, leading to a higher drug concentration at the site of tumor and reduced side effects as compared to the systemic administration (Maeda *et al.,* 2000). Moreover, comparing with current nanodrug delivery systems, such liposomes, nanoparticles and dendrimers, polymeric micelles have improved stability as well as higher

drug-loading capacity. The properties of polymeric micelle system such as solubilization, P-glycoprotein inhibition, selective targeting, subcellular localization etc. makes it popular to receive growing scientific concern for utilizing it as an effective drug transporter. Hence, polymeric micelle systems have become very important in cancer research, and is hoped to be used effectively in cancer therapy.

Niosomes

The formation of niosomes occur at the admixture of non-ionic surfactant of cholesterol or alkyl/dialkyl polyglycerol class of ether, with consequent hydration in the liquid medium. Niosomes are microscopic, have a lamellar structure, are designed like liposomes, and can be used as an efficient substitute for liposomal drug delivery systems (Uchegbu & Vyas, 1998). Figure 7 demonstrates the process of formation of niosomes. They are non-ionic, less toxic, and are found to improve the therapeutic index of medicinal formulations as they can restrict its action in the target cells. For such reasons, they could successfully be used as a transport system for drug delivery. The properties of the formation of vesicles are controllable and variable. Changing size, vesicle composition, surface charge, lamellarity, concentration, and trapped volume can regulate the characteristics of vesicle. The niosomal vesicles works as a depository that releases the drug in a regulated mode. Niosomes demonstrates active osmosis and stability, also, they can enhance the stability of the encapsulated drugs. They are found to increase the oral bioavailability of such drugs that have poor absorption capability and can also increase absorption through skin. The dispersion of niosomes in liquid medium can be made into non-aqueous phase through emulsification for regulating the rate of delivery of drugs to transport normal vesicle into outer non-aqueous mode. Niosomes are used for a wide range of possible medicinal applications such as for anticancer drugs, immunological adjuvants, anti-infective targeting vehicles, diagnostic imaging mediators, and as anti-inflammatory drug carriers. Additionally, the administration of niosomes can be done through many pathways as they are very diverse transportation medium. Some studies have also used niosomes as an efficient approach for delivering transdermal drugs (Choi & Maibach, 2005).

Figure 7. Process of Formation of Niosomes (Aqil et al., 2013).

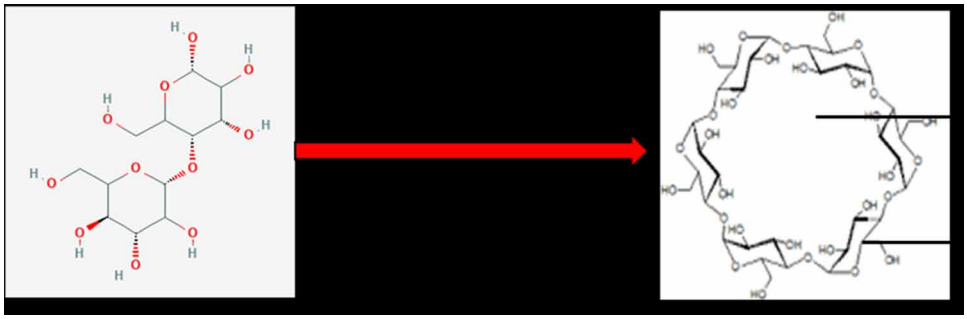


Cyclodextrin

Cyclodextrins are molecules that have distinctive structure, with ‘pseudo-amphiphilic’ nature. Many members of the cyclodextrin family are utilized in the medicinal industry and demonstrate various associated applications. Cyclodextrin, or cyclic oligomers of a-1,4-D-glucopyranoside is formed when the starch gets degraded by the enzyme glucosyl-transferase (Figure 8). Cyclodextrin can interact with

a wide range of other molecules to develop non-covalent inclusion composites because of their unique structure, i.e., hydrophilic outer layer and lipophilic inner core (Challa *et al.,* 2005). The lipophilic (hydrophobic) inner core makes the cyclodextrin able to acclimatize water insoluble molecules. On the other hand, the outer hydrophilic layer makes it friendly for many molecules that are soluble in water. Cyclodextrin have find its wide use in drug delivery applications and are basically utilized for preparing drug delivery medium, like microspheres, nanoparticles, liposomes, and microcapsules.

Figure 8. Formation of Cyclodextrin (Aqil et al., 2013).



The bioavailability of insoluble drugs can be increased by cyclodextrins as they can enhance the dissolution power as well as solubility. The permeability of hydrophobic or insoluble drugs can also be increased by cyclodextrins as they can make the drug accessible at the outer layer of biological membranes such as, mucosa and skin. From there, the drug penetrates into the system without disturbing the lipid bilayer of the outer barrier. In such cases, it is crucial to use just as much cyclodextrin as needed to solubilize the drug in the liquid medium because if used in excess, it can reduce the availability of drugs. The bioavailability of drugs can also get increased with the help of cyclodextrin as they can stabilize the medicinal molecules at the surface of bio membrane. For instance, in case of nasal administration, the cyclodextrin can enhance the bioavailability of insulin because of this stabilizing factor. One of the most effective methods to overcome the metabolism of hepatic first-pass is sublingual drug transportation (Harris & Robbinson, 1992), in which the drug reaches the blood circulation by getting dissolved in the mucosal layer. It has been reported that cyclodextrin can enhance the bioavailability of a lot of lipophilic drugs in sublingual formulations (Uekama & Otagiri, 1987).

Cyclodextrin has a very crucial function in the preparation of such drugs that are insoluble in water as it can improve the dissolution as well as solubility of the drug. Cyclodextrins are referred as 'enabling' medium and can be utilized for delivering both intravenous and oral drugs. When administered orally, cyclodextrin can increase the bioavailability of water insoluble formulations by protecting it from degradation, molecular dispersion, and transportation to the epithelial layer of the intestinal mucosa. When injected intravenously, they act as solubilizes for hydrophobic medicines without changing their pharmacokinetics (Thompson, 1997). Furthermore, some drugs are found to have as association with non-specific hydrophobic forces and can quickly detach at the regions of greater affinity, such as, at the fat-rich layer of the intestinal mucosa after getting ingested orally (Stevens, 1999), or after getting in contact with the plasma proteins during intravenous administration (Stella & Rajewski, 1997).

CONCLUSION

Phytochemicals and other plant based natural compounds have been used as medicinal products by humans since ages. These phytochemicals have shown exceptional chemical diversity, therapeutic potential, biological and chemical properties along with minimal toxicity or side effects. However, despite so many advantages, pharmaceutical industry is reluctant while investing in plant-based medicines. Various hurdles, like its instability, poor solubility, low absorption, poor bioavailability, and paucity of targeted delivery are observed in bringing natural plant compounds to therapeutic use. Another challenge includes prompting further research and creating a database for recommended dosages and correspondingly determine per capita phytochemical demands for public health management. As per World Health Organization (WHO), traditional plant product based medicines fulfill about 80% requirement of the population in developing countries. In developed countries the market is however still dominated by synthetic drugs. Recently, it has been observed, that the requirement of synthetic drugs is reducing, as researchers are concentrating substantially on creation of phytochemical-based medicine, along with the development of advanced approaches related to the carrier system and targeted delivery. One of the major areas of research in future can include identification of the primary markers of diseases that allow fixed targeting without any alterations to the regular cellular process. Enhanced knowledge of diseases at molecular level and understanding their molecular information can stimulate in evolving the area of nanomedicine. Studies regarding controlled release and targeted delivery of drugs, technological assessment of the release, effect of these bioactive compounds at cellular level, as well as mathematical modelling of predication are still in its infancy. Further, apart from considering all the benefits, the potential risk of these carriers to humans as well as the environment cannot be ignored and requires long term studies and analysis.

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Chapter 25
Essential Oils and Their Biological Application in Drug Discovery:
Essential Oil as Potential Drug Leads

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ABSTRACT

Essential oils are plant-derived secondary metabolites that find immense application in the treatment and management of both communicable and non-communicable diseases. These oils exert a wide array of pharmacological and biological properties that are attributed to the various classes of its phytoconstituents. As these phytoconstituents act on multiple cellular targets, they are found to be beneficial in wide range of diseases. To overcome the bottlenecks in allopathy medication and also to minimize their adverse effects, alternative therapies utilizing essential oils and their components gained momentum. The myriad components of essential oils offer potential lead compounds in the drug discovery process. As many essential oils and their components are in Phase III clinical trials, drugs derived from them will protect and promote the health and welfare of mankind.

INTRODUCTION

Essential oils (EO) are complex mixtures of volatile secondary metabolites that are responsible for the aroma and biological properties of plants. The term "essential oil' originated from the Latin expression '*quintaessentia'* which literally means the 5th element. Human interest on essential oils dates back to prehistorical periods where they are referred as the 'soul or spirit' of the plant. From time immemorial essential oils have find immense application in the treatment and management of acute and chronic diseases. They are extracted from various plant parts and exhibit diverse pharmacological properties (Table 34.1 & Figure 34.1). The use of EO to prevent illness and its utilization in religious ceremonies has been documented in historical records of several countries.

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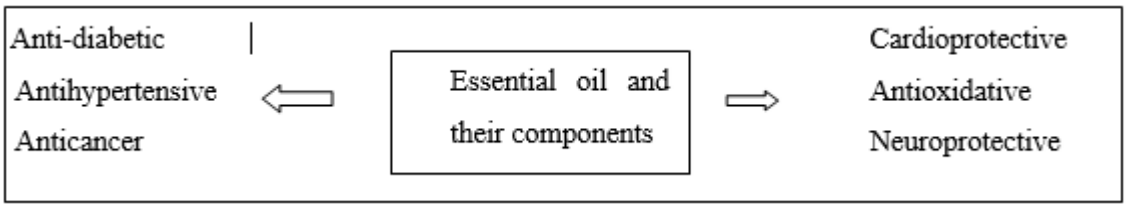
Figure 1. Schematic representation of pharmacological properties of Essential Oil & their components



In plants, secondary metabolism produces a large number of specialized compounds, called secondary plant metabolites that play a vital role in plant health, defense, communication, signaling and in the regulation of primary metabolism. Albrecht Kossel, the Nobel Prize winner in 1910, first proposed the concept of secondary metabolites (SM) in plants. Based on biosynthetic pathway the SM is classified into: terpenoids, phenolic compounds, and alkaloids. Essential oils are composed on terpenoids, phenolics, alkaloids and a wide variety of aromatic and aliphatic compounds which include alcohols, aldehydes, ketones, that are present in variable concentrations.

SECONDARY METABOLITES (SM)

Terpenes

Terpenes and terpenoids are the condensation products of isoprene (2-methyl-1,3-butadiene), a pentacarbonate unit with two unsaturated bonds, and therefore they are alsotermed as isoprenoides. Terpenoids are modified terpenes with different functional groups and oxidized methyl groups. At times, the terms, terpenoid and terpene are used interchangeably by researchers. Terpenoids comprise a large family of plant secondary metabolites synthesized from acetate via the mevalonic acid pathway. They are polymeric isoprene derivatives linked in head and tail fashion. Based on the number of isoprene units they are further classified in relation to the number of five carbon units in their structure as, hemi-(C5), mono-(C10) sesqui-(C15), di- (C20), sester-(C25), tri-(C30) and tetra-(C40: carotenoids) terpenoids. Approximately, more than 40,000 terpenoids have been identified so far (Biswas *et al.,* 2021). Although several thousands of terpenoids were characterized, they are synthesized only by a few biosynthetic pathways. Almost all

Table 1. Plant parts and essential oils

Leaves	Flowers/ Buds	Seeds
Bergamot	Ylang Ylang	Nigella sativa
Tea tree	Clove	Cumin
Mint	Jasmine	Cardamom
Cinnamon	Chamomile	Coriander
Eucalyptus	Rose	Nutmeg
Lemon	Neroli	Fennel

of them have pharmacological properties and are used for the treatment of numerous diseases. In addition, flavors and fragrances of terpenoids play a key role in pest control. Certain terpenoids are highly volatile and reactive in nature and thus involved in plant-plant interaction, signaling between symbiotic organisms, and the attraction of pollinating agents (Boncon *et al*., 2020).

Alkaloids

Alkaloids are huge and diverse group of SM, mainly found in vascular plants. Till now, approximately 15,500 alkaloids have been isolated from plants. They essentially contain nitrogen atom and possess neutral/weakly acidic properties and contain oxygen, sulfur, phosphorus, bromine and chlorine. They have wide range of pharmacological activities (Mitra *et al*., 2021). As structurally they are diverse, there is no clear-cut classification between alkaloids and other natural nitrogen compounds (except, for instance, nucleotides, amines etc.). Tyrosine is the precursor for the biosynthesis of alkaloids. Classification of alkaloids is based on numerous criteria such as, biosynthetic origin, existence of basic heterocyclic nucleus, pharmacological activities and distribution among plants. However, classification based on biosynthetic origin is frequently followed, and the alkaloids are classified as-true, proto and pseudoalkaloids. True alkaloids are synthesized from L-forms of amino acids such as, ornithine, lysine, tyrosine, tryptophan, histidine and arginine. Protoalkaloids (aromatic amines) are less in number and synthesized form L-forms of tyrosine, tryptophan and ornithine. Pseudoalkaloids are alkaloid like compounds and are not synthesized from amino acids (Liu *et al*., 2019).

Phenolics

Phenolics are the largest group of plant SM, primarily contain hydroxylated aromatic rings. Phenolic acids are esters or glycosides are conjugated with flavonoids, sterols, hydroxy-fatty acids, alcohols and glucosides. Malonate/acetate or shikimic acid pathway is the key route of biosynthesis of phenolic compounds. Plant phenolics are classified in three different ways: i) Number of hydroxylic groups present; (ii) Chemical composition and (iii) the nature of substitutes in C skeleton. Of late, phenolic compounds are classified into compounds with one aromatic ring, two aromatic rings, quinones and polymers. Polyphenols are phenolic compounds containing one or more hydroxyl group in the aromatic ring. Flavonoids are poly-hydroxylatedpolyphenolic compounds with 15 carbon atoms. They are subdivided into flavones, flavanones, isoflavonoids, anthocyanins and anthoxanthins based on degree and position of hydroxylation. Phenolics are key antioxidants, and they act as plant growth inhibitors in seeds (Zhang *et al.,* 2022).

Phenylpropanoids

Phenylpropanoids contain one or more C6–C3 units, with C6 being a benzene ring having a methyl ether functional group attached to the ring, and a propenyl tail. Many of the phenylpropanoids found in EOs are phenols or phenol ethers. Most of the constituents of EO falls under terpenes and phenylpropanoids.

EXTRACTION PROCEDURES

Advances in extraction and characterization techniques, documented the chemical profile of essential oils. The extraction of EO from natural products falls under two categories.

Classical or conventional methods:

- Hydrodistillation
- Entrainment by water stream
- Organic solvent extraction
- Cold pressing

Innovative Methods:

- Supercritical fluid extraction
- Subcritical extraction liquid
- Ultrasound assisted extraction
- Microwave assisted extraction
- Instant controlled Pressure drop

The choice of the extraction method is determined by the type, quantity, and stereochemical structure of the essential oil molecules and also on the geography and nutritional status of the plants. The extraction method can also lead to significant modification of the chemical profile of the essential oil. The composition, concentration of essential oil depends on several intrinsic and extrinsic factors. The intrinsic factor includes genetics, physiology, physiological and biochemical pathway of the plant, season of sampling and stage of development. External factors include environmental factors, cultivation methods, postharvest techniques and quantification procedures. A variety of techniques are employed for chemical characterization of essential oils. Gas chromatography is the preferable choice for chemical profiling due to the volatile nature of EO. However other tools like mass spectrometry, NMR and IR are used in addition to Gas Chromatography (Fan *et al*., 2018).

As essential oils contain a myriad of components with diverse functional groups, they act on multiple cellular targets and are helpful in virtually all forms of disease etiology. The pharmacological activities of these oils were attributed to the synergistic and/or additive effects of the chemical constituents. Recent scientific evidence on therapeutic properties of essential oils have invoked increased interest in its use in alternative medicine. Being lipophilic in nature, essential oil components efficiently cross the blood brain barrier and exhibit psychoactive effects. Further oral or nasal applied essential oil, rapidly sink into adipose tissue and some components circulate in blood via albumin. In addition, essential oil components potentiate the efficacy of other drugs by increasing intercellular diffusivity (Sadgrove *et al*., 2021).

THERAPEUTIC APPLICATIONS OF ESSENTIAL OILS

Diabetes Mellitus and Essential Oils

Among the various noncommunicable diseases, diabetes mellitus (DM) has become an epidemic worldwide and according to WHO, it is the ninth leading cause of death worldwide. Diabetes mellitus is a chronic metabolic disorder with altered carbohydrate, protein and lipid metabolism arising from defective secretion/ action of insulin. Deranged metabolism with sustained hyperglycemia impairs the function of pancreatic β-cell and brings pathological changes in several tissues. Diabetes has become a major cause for cardiovascular, cerebrovascular and peripheral vascular diseases. The global prevalence of diabetes mellitus is around 415 million in 2015 which is expected to rise 642 million by 2040 (Ogurtsova *et al*., 2017). In India, the prevalence of diabetes mellitus is between 5-17% with higher incidence in southern part of the country. The scenario of diabetes has changed from the disorder of elderly to the major cause of morbidity and mortality in the youth and middle-aged people. Genetic, environmental and lifestyle modification are major risk factors in the onset of diabetes mellitus. According to WHO, DM has been aggravated due to rapid cultural and social dynamics, ageing population, lifestyle and behavioural changes with reduced physical activity. As the prevalence is especially rising more rapidly in low- and middle-income countries than in high-income countries, there is a globally agreed notion to halt the rise in diabetes and obesity by 2025 (Magliano *et al*., 2019).

India is one of the epicenters of the global diabetes epidemic and has the second highest number of people with the disease. The commonly employed medications for diabetes mellitus include

- Insulin
- Alpha-glucosidase inhibitors
- Biguanides
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 receptor agonists
- Meglitinides
- Sodium-glucose transporter (SGLT) 2 inhibitors
- Sulfonylureas
- Thiazolidinediones

The main objective of medication in diabetes mellitus is to reduce hyperglycemia and minimize the risk of vascular complications. Currently available oral hypoglycaemic drugs used for the management of diabetes are often associated with undesirable side effects or diminish in their response after prolonged use. Moreover, these drugs target unique targets i.e., for instance they either enhance insulin secretion or improve insulin sensitivity. This has led to the introduction of combination therapy for the management of diabetes mellitus, as they focus on multiple targets. Recently it has been discovered that essential oils improve glycemic status and reduce the severity of complications in both type-1 and type-2 diabetes mellitus. Mounting evidence suggest that essential oils play a pivotal role in the management of diabetes mellitus. Many of them are found to enhance insulin secretion from pancreatic β-cells and also improve insulin sensitivity in target cells thus circumventing the need for multidrug therapy. Essential oils ameliorate free radicals and improve endogenous antioxidant capacity and thus curtail the risk of diabetic complications. Further they activate peroxisome proliferated activated receptor subtypes, PPAR-α and

PPAR-γ and ameliorates dyslipidemia and insulin resistance. Several studies on experimental diabetic models highlighted that essential oils exhibit anti-glycation properties and modulated the activities of key rate limiting enzymes and restored metabolic homeostasis. These actions are attributed to the multiple pharmacological mechanisms of essential oils. Based on the available experimental evidence, several hundreds of essential oil exhibit antidiabetic potential. Listing all of them is beyond the scope of this chapter and hence few examples that focus on diverse aspects are listed below:

1. Essential oil from the seeds of *Momordica charantia* L. enhanced insulin secretion, ameliorated diabetic dyslipidemia and restored renal function in STZ induced diabetic rats (Mariammal *et al.,* 2021). The essential oil of nigella sativa improved antioxidant status and curtailed lipid peroxidation in diabetic rats (Sultan *et al.,* 2014).
2. Diabetes is associated with hyperalgesia due to nerve damage and changes in signalling pathways. Essential oils from *Melissa officinalis* restored glycemia and decreased the intensity of nociceptive behavior, thus confirming its role in the management of painful diabetic neuropathy (Hasanein & Riahi, 2015). Essential oil of *Croton zehntneri* prevented alterations of the vagus nerve in diabetic rats (Silva-Alves *et al*., 2021).
3. Inhibition of intestinal carbohydrate metabolic enzyme helps in decreasing the absorption of dietary carbohydrates. Essential oils from *A. melegueta* and *A. danielli* seeds inhibited α-amylase, α-glucosidase and angiotensin-I-converting enzyme in vitro and thus exhibiting antidiabetic and antihypertensive effects (Adefegha *et al.,* 2017).
4. Diabetes induced oxidative stress is associated with structural and functional alterations in the germ cells of testis. Activation of JNK pathway and Bcl2 causes testicular injury and apoptosis. By strengthening the antioxidant defence mechanisms, *Solanum lycopersicum* seed essential oil attenuated the adverse effects on reproduction (Kermani *et al*., 2019). In addition, erectile dysfunction is a debilitating condition among diabetic men. The essential from clove essential caused corpus cavernosum relaxation via potassium channels independently of nitric oxide signalling pathway (Yilmaz-Oral *et al.,* 2020).
5. Essential oil from lemongrass improved adipocyte metabolism and curtailed obesity the most common predisposing factor for diabetes mellitus, hypertension and coronary artery disease. At the molecular level, lemongrass essential oils ameliorated the disturbed expression of key the transcription factor sterol response binding protein 2 and its targets in adipocyte cell lines (Sprenger *et al.,* 2022).
6. The process of wound healing occurs on sequential phase's viz., inflammatory, proliferative and remodeling which takes its own time. Various factors such as nutritional status, immuno deficiency, chronic diseases, and vascular insufficiencies delay or impede wound healing. Ultimately the healing process depends on the differentiation of fibroblasts and biosynthesis of new collagen fibers. Essential oil of *Bursera morelensis* enhance the healing process by promoting the migration of fibroblast and remodeling of collagen at the wound site (Salas-Oropeza *et al*., 2020). In a similar fashion, nanoparticles synthesized with essential oil of *Homalomena pineodora* inhibited microbial growth in diabetic ulcers (Rozman *et al*., 2020).
7. Essential oil based oral rinse is found to be effective during scaling and root planning procedures in diabetic patients. As an adjuvant it helped in the treatment of periodontal inflammation in type-2 diabetic patients (Alshehri *et al*., 2015).

Cardiovascular Diseases (CVDs) and Essential Oils

Cardiovascular diseases (CVD) are one of the most common non-communicable diseases (NCDs) that are responsible for a large number of morbidity and mortality. CVD refers to all those conditions that affect the structure and function of heart. According to WHO, an estimated 32% global deaths are due to CVD and the common risk factors for CVD are hypertension, vascular diseases, tobacco use, unhealthy diet, obesity, alcohol abuse, physical inactivity, dyslipidemia and diabetes mellitus. Further the role of oxidative and inflammatory stress on the pathogenesis of heart disease has been well documented. Oxidative stress also contributes to vascular dysfunction by inhibiting nitric oxide (NO) and endothelium-derived hyperpolarizing factor mediated relaxation of the arteries. A worsened redox state or or derangement of vascularfunction contributes to chronic cardiovascular disease. Essential oils and their constituents have shown promising results a therapeutic agent to treat cardiovascular diseases.

The prevalence of hypertension in adults is rising at an alarming rate and its management is primarily focused on lifestyle modifications and antihypertensive drugs. However, the long duration of pharmacotherapy and subsequent organ damage poses a need to search for alternative therapeutic modalities. Many complementary and alternative medicines reduce hypertension by lowering sympathetic nervous system activity. A number of essential oils are considered as cardiac tonics and exert a positive effect on blood pressure maintenance and on general health.

Inhalation of essential oil blended with lavender, ylang-ylang, marjoram, and neroli in the ratio of 20:15:10:2, decreased salivary cortisol levels and systolic blood pressure. Their actions are found to be immediate and continuous in controlling blood pressure and stress reduction. In stage 1 hypertensive patients aroma therapy with lavender, ylang-ylang, and bergamot decreased BP and in a separate study, lavender aromatherapy in prehypertensive middle-aged women decreased BP and restored the balance in autonomic nervous system (Hwang, 2006). Studies have shown that slight decrease in SBP (2mmHg) can lead to a decrease in mortality due to coronary artery disease and stroke by 7% and 10%, respectively. Thus, essential oil inhalation is found to be an effective intervention for BP control. Further, continuous essential oil therapy aids in the balance of autonomic nervous system by controlling stressors. Essential oil of *marjoram* stimulates parasympathetic nervous system and controlled stress and BP in hypertensive patients (Kim *et al*., 2012).

Vasoconstriction is one of the major contributors of hypertension. The hypotensive potential of several essential oils (*Lavender, Ocimum gratissimum L, Mentha x villosa Huds, Artemisia campestris, Rosa indica L.*) was studied in preclinical trials and the targets through which they exert their effects fall under the following:

- Modulation of vanilloid receptor subtype 1 (TRPV1)
- Modulation of muscarinic and nicotinic acetylcholine receptors
- Nitric oxide (NO) axis
- Modulation of L-type Ca^{2+}channels
- Activation of SERCA pumps
- Phosphorylation of eNOS via intracellular Ca^{2+}/protein kinase A (PKA)/eNOS pathway
- As COX inhibitor

Intake of diet rich in saturated and trans-fat, increased levels of total serum cholesterol, low density lipoprotein cholesterol increase the risk of cardiovascular diseases. Often dyslipidemia is associated with

CVD. In the presence of co-morbid conditions such as hypertension, unhealthy lifestyle and dyslipidemia brings disturbances in cholesterol metabolism thus increasing the susceptibility to stroke and CVD. Agents that retard the intestinal absorption of lipids, inhibitors of rate limiting enzymes of cholesterol/ lipid metabolism, and modulators of transcription factors governing the expression of lipid metabolic enzymes are helpful in combating dyslipidemia and CVD. Essential oils that ameliorate lipid metabolism are powerful agents in controlling CVD. Studies have revealed that essential oils (*Acorus calamus* L. *Salvia officinalis* L. *Cinnamomum tamala, Plantago asiatica* L., and *Cumin* etc.) modulate peroxisome proliferator activated receptor-α and modulate the genes associated with transport and metabolism of lipids. Some of the essential oils increase LDL clearance by increasing the affinity of LDL receptor (Mollace *et al*., 2008; You *et al*., 2013).

Platelets have a well-defined role in atherosclerotic process and play a critical role in the pathophysiology of CVD. Platelets adhere to the injured vascular endothelium with subsequent release of proinflammatory mediators initiating a vicious of events that promotes atherosclerotic process. Studies have revealed that essential oils inhibit platelet aggregation and prevent atherosclerosis and subsequent cardiovascular events. The mechanisms are mediated by inhibition of cyclooxygenase-1 and 2, delaying the formation of platelet plug etc. Some of the important essential oils with potent antiplatelet aggregation activity are *Ocimum basilicum, Origanum vulgaris* L., *hymus vulgaris* L., *Artemisia campestris L Artemisia dracunculus* L. etc. (Tognolini *et al*., 2006).

Cancer and Essential Oils

Cancer is a major public health problem and is the second leading cause of death worldwide. Several factors such as race, gender, age, genetics, and environmental factors influence the incidence of cancer. The burden of cancer exerts enormous physical, emotional and financial constraints and large number of cancer patients especially in low- and middle-income countries can't gain access to early diagnosis and quality treatment. Cancer can arise in any organ or tissue in the body and is associated with unregulated and unrestricted growth of cells. In response to various internal and external stimuli alterations occur at the molecular level in the cancer cell leading to the following

- Capacity to proliferate without any growth signals
- Resistance to growth inhibiting signals
- Resistance to cell death mechanisms
- Increased angiogenesis
- Metastasis

A multidisciplinary approach involving chemotherapy, radiotherapy, surgery, immunotherapy or a combination of all are employed for the treatment of cancer. Studies have documented that essential oils exhibit anticancer effect in both *in vivo* and *in vitro* experimental models (Nie *et al*., 2016). Breast, colorectum, lung, cervix, and thyroid cancer are the most common cancers among women while prostate, stomach, and liver cancer are common types among men.

Breast cancer is the most common malignant disease among women and is associated with high morbidity and mortality. Based on the type of cell that is being affected, there are different types of breast cancer viz., Ductal carcinoma, Ductal carcinoma in situ (DCIS), Invasive or infiltrating ductal carcinoma, Invasive lobular carcinoma, inflammatory breast cancer and Paget's disease. Chemoresistance

and toxicity are the prominent cause of failure in the treatment of breast cancer. In this context, Human Caucasian breast adenocarcinoma cell lines (MCF-7) were subjected to serial dilutions of frankincense, pine needle and geranium essential oils to study their anticancer effects. It has been found out that these essential oils suppressed the migration of cell lines and induced apoptosis. AMPK is the central energy-sensing system that coordinates cellular metabolism and cancer progression through mTOR signaling mechanism (Athamneh *et al.,* 2020). Essential oils regulated AMPK-initiated mTOR inhibition confirming its antiproliferative, antiinvasive and apoptotic effects. A major obstacle in successful chemotherapy is the development of multidrug resistance (MDR) in cancer cells. It arises from different mechanisms that include interplay of several factors involving the down regulation of drug targets, expression of drug resistance genes, dysregulation of cytokines and up-regulation of transporters especially ATP-binding cassette (ABC) transporters which extrude chemotherapeutic drugs from cancer cells. Compounds that act as MDR reversing agents may help in circumventing drug resistance and improve chemotherapy. Recently essential oils have emerged as promising agents in reversing MDR as they target multiple signaling mechanisms. Essential oil from Tea tree inhibited the interaction of ABC transporters with membrane components and their intracellular signaling thereby preventing the cell migration in MDR melanoma cells (Bozzuto *et al.,* 2011). In multidrug-resistant breast cancer cell model (MCF-7/ADR), essential oils of *Angelicae dahuricae* (ADO) and *Inula japonica* (IJO) downregulated ABCB1expression and reduced lipid raft stability and thus exerting a safe and effective MDR reversal agent (Zu *et al*., 2010).

Prostate cancer is the most commonly diagnosed cancer among men. Abnormal signaling/disruption of androgen signaling, fusion of oncogenic proteins TMPRSS2 (Transmembrane protease, serine 2) with ERG (ETS-related gene) contributes to the metastatic progression of prostate cancer (Hossain *et al*., 2013). Essential oil of *Lavandula angustifolia* Mill (Lamiaceae) and its active ingredient linalool effectively inhibited human prostate tumor growth and proliferation and induced apoptosis (Zhao *et al*., 2017). The essential oil of *L.angustifolia* also exhibited apoptotic effects on cervical cancer (HeLa), prostate cancer (PC-3), human lung cancer (A-549) and on breast cancer (MCF-7) cell lines (Zu *et al*., 2010). Essential oils from the flowers and leaves of *Callistemon citrinus* induced apoptosis and exhibited antiproliferative effects in lung carcinoma cell line A549 and rat glioma C-6 cells.

The therapeutic effect of EO on diverse cancer falls on two broad mechanisms. They are being: chemoprevention and suppression. Currently various modalities ae employed for cancer treatment which includes modulation of DNA repair mechanisms, activation of detoxifying enzyme and prevention of metastasis and angiogenesis. As EO acts on various targets they cause cell cycle arrest, enhance apoptosis, reduce proliferation and metastasis. This makes EO a potential candidate for cancer therapy. Essential oils of the following species are documented as anticancer agents are

- *Azadirachta indica*
- *Thymus broussonetii*
- *Salvia libanotica*
- *Thymus broussonetii*
- *Citrus aurantifolia*
- *Rosmarinus officinalis*
- *Hibiscus cannabinus*
- *Cinnamomum zeylanicum*
- *Murraya koenigii*

Respiratory Diseases and Essential Oils

Respiratory diseases are one of the biggest challenges to health and human activity. These diseases affect the lungs and airway systems making breathing a difficult task. Respiratory infections are the single largest contributor for respiratory disease and it accounts for more than 4 million deaths annually across the globe. The most alarming respiratory conditions are asthma, acute respiratory infections, chronic pulmonary obstructive disease, tuberculosis and lung cancer. Respiratory infections of viral origin can occur as pandemic and spread across communities. Prevention and treatment for these diseases has been given the topmost priority with particular focus on their affordability and availability to general public. The diverse pharmacological activities such as antiviral, antibacterial, anti-inflammatory, antioxidant and immune modulatory effects restrict viral entry, inhibit viral replication, and enhance bronchodilation and mucolysis. Essential oils and their components are traditionally being used to treat respiratory tract infections and disorders.

Asthma and Essential Oil

Atopic asthma initiated by the exposure to allergens and bronchial asthma arising from hypersecretion of mucous cause airflow obstruction, hyper responsiveness and inflammation. Upregulation of the predominant gel forming mucins MUC5ac and 5b are responsible for asthmatic inflammation. Inhalation of Lavender essential oil suppressed inflammatory cell accumulation in peribronchial and perivascular tissues in murine model of asthma. In yet another study the essential oil of *Nepetacataria* through inhibiting calcium channels and phosphodiesterase activity causes relaxation of respiratory muscles and exhibits a promising agent for asthma (Gilani *et al*., 2009). In experimental asthmatic model involving mice, essential oil from *Abies holophylla* leaf (EOA) decreased air way inflammation, hyperplasia of respiratory epithelium and goblet cell activation. Further inhalation of essential oil decreased NF-kB, TRAF6 and MAPK and increased Treg cells related cytokines through IL-17 related signaling pathway (Park *et al*., 2022).

Respiratory Infections

Several bacterial and viral strains causing respiratory infections isolated from throat swab includes: *Streptococcus pyogenes, Staphylococcus aureus, Haemophilus influenzae, Stenotrophomonas maltophilia* and *Klebsiella pneumoniae*, adenovirus and mumps virus etc. Essential oil from eucalyptus is found to exhibit antibacterial and antiviral effects on the respiratory pathogens (Cermelli *et al*., 2008). Currently, essential oils of geranium and lemon have found to downregulate ACE2 expression in lung epithelial cells and prevent COVID-19 infection (Senthilkumar *et al*., 2020). Essential oils from garlic potentiate Nrf2 activation and downregulated cytokine genes and controlled 'cytokine storm' during COVID19 infection. The components in garlic essential oil prevented the entry of virus into host cells by down regulating the expression of both ACE2 and TMPRSS2. Inhalation of essential oils to treat upper respiratory tract infections especially bronchitis and sinusitis has been practiced since time immemorial. Inhalation of essential oil of *Artemisia capillaris* brought morphological changes and enhanced the activity of ion channels thereby promoting the leakage of ions (potassium and phosphate) from bacterial cells causing significant antibacterial effects. In *in vitro* models, *Luofushan-Baicao* Oil (LBO) downregulated NF-κB

P65, IRF3and decreased the expression of interleukins (IL-1β, IL-6), and interferon-β thereby acting as a potent agent against influenza (Mao *et al*., 2021).

Chronic Pulmonary Obstructive Disease (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a persistent and progressive inflammatory lung disease characterized by irreversible airflow obstruction with difficulty in breathing, cough and/or phlegm production. In an experimental model of COPD, rats administered with spearmint essential oil showed reduced leucocyte numbers in bronchoalveolar lavage fluid, attenuation of bronchiolitis and inflammation. It also enhanced the expression of Nrf2 protein and reduced MDA levels in lung tissues (Zhao *et al*., 2008). Neutrophil elastase causes extensive tissue damage and malfunctioning of airways resulting in the development of COPD. Essential oil from *N. sativa* inhibits elastase activity and acts as a natural antielastaseagent in the treatment of COPD (Kacem & Meraihi, 2006).

Tuberculosis and Lung Cancer

Mycobacterium tuberculosis, the causative agent of tuberculosis has developed resistance to most of the currently available antimicrobials. The increasing incidence of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis urges the need to search for new anti-TB agents. Essential oil from the leaves of *Ocimum sanctum* inhibited the growth of H37Rv the most studied strain of tuberculosis and all the nine clinical isolates of M. tuberculosis (Jayapal *et al.*, 2021). Further, essential oil from aerial parts of *Pulicaria gnaphalodes* and *Perovskia abrotanoides* flower were found to be effective against sensitive isolates of MTB and MTB H37Rv (Hozoorbakhsh *et al*., 2016). Exposure of mycobacteria to cinnamon essential oil lowered the cell wall permeability, membrane fluidity and disturbed redox homeostasis. These antimycotic effects of essential oil are attributed to cinnamaldehyde, the main ingredient (Sieniawska *et al*., 2020).

Nervous System Disorder and Essential Oils

The nervous system is vulnerable to vascular, structural and functional disorders, infections, degenerative and autoimmune disorders. Neuro-pharmacological properties of essential oils led to its wide application in the treatment of nervous system disorders. It has been suggested that EO and their components are more effective in mitigating the mental illness and exert sedative, hypnotic and anti-depression effects. As a complementary therapy, essential oil improves anxiety, insomnia, and cognitive function. Administration of EO via different routes such as inhalation, ingestion or topical are practiced in many countries as prophylactic care or for treatment. At appropriate concentration the pharmacological effects of EO are safer than commercial psychotropic drugs (Mendes Hacke *et al*., 2020).

According to WHO, depression and anxiety disorders are the most prevalent mental illness across the globe. It has been reported that depression is the single largest contributor for suicide ranking it in the top 20 places of death worldwide. It has been confirmed that psychostimulant EOs interact with the ascending neurotransmitter and induce alert waking stage in the forebrain through activation of neurotransmitter network. More specifically the inhalation of essential oil stimulates brain to release neurotransmitters through olfactory system and regulates mood and behavior. Psychological stress, depression and anxiety are associated with insomnia. Derangements in the secretion of neurotransmitters like 5-hydroxytryp-

tamine (5-HT) and gamma-aminobutyric acid (GABA) are closely associated with insomnia. Several studies have documented that the neuro-pharmacological effects of essential oils are attributed to its modulatory effect on GABAergic system and Na^+ channels (Wang & Heinbockel, 2018). To maintain the overall balance between neuronal excitation and inhibition for normal brain function activation of the γ-aminobutyric acid (GABA) receptor system and the blockade of neuronal voltage-gated sodium channels are essential. In this context, inhalation of compound Anshen essential oil increase the content of 5-HT and GABA in the brain of mice and reduced latency and prolonged the sleeping time indicating the sedative and hypnotic effects of essential oil. Based on network pharmacological studies the essential oil of Anshen regulates 5-HTand GABA levels through targeting calcium signaling pathway, cholinergic and GABAergic synapse pathways. Inhalation of essential oils is an effective and rapid way to control/ treat insomnia as it induces central nervous system within 4 sec. Further administration of essential oil via inhalation is a nondestructive process that minimizes toxic side effects (Ren *et al*., 2019).

In age related disorders such as Alzheimer's disease, the formation of amyloid-β plagues and neurofibrillary tangles are associated with increased activity of acetylcholinesterase which reduce acetylcholine, a neurotransmitter essential for learning and memory. This decrease is followed by synaptic alterations, chemical and biological changes, inflammation of brain and cognitive impairment. Recent evidence reveals that constituents of essential oils improve cognitive function by exhibiting acetylcholinesterase inhibitory activity (Agatonovic *et al.,* 2019). Synucleinopathies are group of neurodegenerative disorders such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), pure autonomic failure (PAF), and multiple system atrophy (MSA) that are characterized by intracytoplasmic accumulation of fibrillary aggregates of α-synuclein protein in selective populations of neurons and glia. α-Synuclein is a highly conserved protein, strongly expressed in the presynaptic terminals of neurons and transported predominantly in the slow component. Retardation of α-synuclein axonal transport leads to accumulations of the protein over time, predisposing to synucleinopathies. Aggregated form of α-Synuclein containing intracellular inclusions exists in synucleinopathies that contributes to degeneration of neuronal populations and is a hallmark of Parkinson's disease and dementia. Parkinson's disease (PD) is the second most common neurodegenerative disease which is attributed to the loss of dopaminergic neurons in the S*ubstantia nigra* resulting in loss of coordination and movement. In the past one decade, a total of approximately 69 EOs from various plant sources were studied for their effectiveness against the common neurodegenerative diseases. Some of the EO that are found to be effective against neurodegenerative diseases are

- *Salvia* species – AChE inhibitory property
- *Lavandula spp* -AChE inhibition and modulation of central neurotransmitter pathways
- *Cinnamomum zeylanicum*- Cholinesterase inhibition
- *Citrus limon*-Decrease neuronal apoptosis; increase in the expression of CaMKII/CREB/Bcl-2.
- *Ocimumbasilicum*- Upregulate brain-derived neurotropic factor
- *Eryngium*- MAO inhibition
- *C. cyminum* - inhibition of α-Syn fibrillation
- *Foeniculum vulgare* - Protective effect on dopaminergic neurons (Bhatti *et al.,* 2018)

ESSENTIAL OILS AND DRUG DISCOVERY PROCESS

With advances in modern medicine and its efficacy, essential oils moved from the mainstay of treatment to the realm of alternative or complementary medicine. Currently, due to the adverse effects of allopathic drugs especially for treating chronic diseases, a shift in approach to natural therapy has gained momentum. Further restriction in the use of chemicals also led to a renewed interest in the discovery of drug from natural sources. The use of medicinal plants and their products has long existed in different cultures across the globe. Essential oils are forming an integral aspect in new drug discovery. They offer a pool of potential compounds for lead generation and hence it deserves more attention. The pleiotropic properties, novel chemistry and chemo types of essential oil components offer a remarkable opportunity for the discovery of new drugs. Drug discovery and development is an expensive and time-consuming process since many lead may fail in the optimization step of drug discovery pipeline. In drug development process, filtering of large number of compounds to viable lead is a cumbersome process. This process of filtering lead compounds termed as Drug Discovery Filter (DDF) that involves the rational analysis of parameters commonly described as Drug Discovery parameters. As many of the active components of essential oil meet the drug discovery parameters, essential oil opens new avenues in drug discovery process. Essential oil components (EOC) have unique properties rendering them suitable for therapeutic applications in diseases of central nervous system, respiratory ailments and for transdermal applications. Research on essential oil is based on bioactivity guided fractionation to identify fractions with potential activities that can be developed to form drug candidates. Recent studies have documented a total of 6412 EOC from 175 different essential oils. These components were analyzed for bioavailability, lead-likeness, fragment-based drug discovery, and drug-likeness and it was found out that 627 attained the criteria of DDP. Approximately 94% of EOC pass out four of the total six DDFs and these results are promising and prove the notion that essential oils are untapped potential in drug discovery process. To explore the multivariate applications of essential oils intensive research concerning the safety, drug interactions, efficacy, and dosage regime need to be carried out before its inclusion in pharmacological arsenal. Keeping in mind, several clinical trials demonstrating the beneficial effects of certain essential oils are carried out.

Essential Oils in Clinical Trials

Clinical trials on the effect of inhaled essential oils of ginger, German chamomile, and bergamot on quality-of-life concerns in patients undergoing chemo, immunotherapy for cancers such as gastrointestinal, skin and neuroendocrine carcinoma were studied. The study confirmed that these essential oils improved the quality-of-life issues such as nausea, anxiety, loss of appetite, and fatigue in patients undergoing treatment for cancer. In chemotherapy induced peripheral neuropathy in breast cancer, an essential oil blend composed of *curcuma longa, Piper nigrum, P. asperum, Zingiber officinale, Mentha x piperita,* and *Rosmarinus officinalis and Simmondsiachinensis* were found to be moderate pain signal via non-competing inhibition of 5-HT, AChE, and Substance P, along with antagonism of the transient receptor potential vanilloid 1 and ankyrin 1 (TRPV1 andTRPA1). Chemotherapy induced nausea and vomiting observed in breast cancer patients were significantly curtailed by the inhalation of peppermint and ginger essential oils. In a similar manner, essential oil mixture of peppermint and sweet almond reduced the severity of nausea, vomiting and retching in cancer patients. The effect of essential oils of peppermint, lavender, or chamomile improved insomnia, pain, lack of appetite, anxiety and depression in newly diag-

nosed acute leukemia patients undergoing chemotherapy. Lavender Essential oil improved sleep quality and metabolic parameters in Type 2 diabetic patients. Psychosis, depression, apathy and agitation are the spectrum of symptoms observed in patients with BPSD. Apart from depression, the study also focuses on brain derived neurotropic factor (BDNF), antioxidant status and amyloid proteins. A study examining the efficacy of Ylang-Ylang (Cananga Odorata) essential oil on dementia related behavioral changes in patients with Behavioral and Psychological Symptoms of Dementia. The essential oil of *Ylang-Ylang* is found to have a calming effect and is a powerful mood regulator (Clinical trial NCT05034107). Abuse of inhalants among young adults is common which leads to the suppression of central nervous system. Currently no therapeutic agents are available to curtail this toxin dependence. As a substitution therapy, EO from *Lavandula angustifolia* was studied for their efficacy against cue –induced craving in toxin dependent patients. The results are promising and inhalation essential oil reduces craving for inhalants (Clinical trial NCT 04874857).

Depression is a common psychiatric disorder which is characterized by mood swings, loss of interest and hope. It is the leading cause of mental illness and disability. The bottleneck in the treatment for depression has to be addressed to minimize the complication. Inhalation of essential oils from Chinese medicinal herbs, *Atractlodis rhizoma, Herba agastaches, Flos caryophylli* are found to exert potent anti-depressive effects. Clinical trials for the treatment of acute viral Laryngitis and Rhinosinusitis with a spray containing aromatic essential oils of *Eucalyptus citriodora, Eucalyptus globulus, Mentha piperita, Origanum syriacum,* and *Rosmarinus officinalis* were carried out. These EOs exerts a direct effect on respiratory tract, decreased the coughing reflex and increased airflow through the nasal tract. These pharmacological properties are attributed to the anti-inflammatory and antimicrobial activities of essential oils (Clinical trial NCT 00611390).

COVID 19 infection is associated with anosmia with persistent olfactory dysfunction even after recovery. An olfactory training therapy with the essential oils of rose, eucalyptus, lemon and cloves were under progress. Gargling to eliminate SARS CoV-2 has been advised to the general public as a measure to protect themselves from the pandemic. Results of the trial proved that gargling with essential oil significantly prevented viral attachment in the throat and nasopharynx highlighting the importance of gargling and essential oils. The COVID19 pandemic has created havoc and caused anxiety among individuals across globe. To reduce anxiety and subsequent mood disorders few drops of a blend of essential oils from citrus plants and flowers were given and their efficacy was studied. The results highlighted the effect of aromatherapy on COVID-19 infection. In addition, essential oils are also found to be effective as oral rinses for the inactivation of COVID-19 infection.

CONCLUSION

From the above, it is evident that a new surge in scientific documentation of the biological/ pharmacological properties of essential oils and their application in the treatment of wide range of diseases have gained momentum. Nowadays a larger of essential oil and their components are available in the market as dietary supplements. As clinical trials proved the safety and efficacy of numerous essential oils new drugs based on them will benefit mankind in the near future.

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