Handbook of Research on

Natural Products and Their Bioactive Compounds as Cancer Therapeutics

Ashok Kumar Pandurangan, Suresh Kumar Anandasadagopan, and Fahad Abdulrahman Alhumaydhi

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strategies for breast cancers as well as strategies to overcome increasing resistance to hormonal and targeted therapy. This chapter focuses on chemopreventative and anti-cancer activities of different bioactive compounds obtained from dietary sources, herbal approach, and use of natural compounds such as diindolylmethane, biochanin A, curcumin, Epigallocatechin Gallate, genistein, lycopene, shikonin, sulforaphane, and resveratol. Understanding the pathophysiology of action of these compounds and their potential preventive and therapeutic effects on cancer may provide a rationale for further studies.

Breast cancer is an aggressive and primary cause of death among women globally. Triple negative breast cancer (TNBC) is one of the sub types of breast cancer. TNBC lacks the expression of progesterone receptor (PR), estrogen receptor (ER), and human epidermal factor 2 (HER2), which leads to poor diagnosis resulting in lack of targeted therapies. On the other hand, natural products are also cost efficient, non-toxic, and abundantly available in nature. Natural products have also been reported to exert various pharmacological activities including cardioprotective, anti-diabetic, antimicrobial, anti-inflammatory, etc. In this chapter, summarization of 12 well known natural products such as chebulinic acid, maslinic acid, apigenin, piperlongumine, Liquiritigenin, berberine, icariin, bufalin, which are targeted against TNBC through regulation of different pathways, and their mechanism are briefly explained. These natural products are already used to treat various diseases at the preclinical level and also have shown to have effective anti-tumor effect and can act as potent anti-TNBC agents.

Colorectal cancer (CRC) is one of the common types of cancer affecting humans. The treatment of CRC involves surgery and chemotherapy. CRC treatment using the conventional chemotherapeutics has a negative burden on the patient's health as a result of high toxicity, occurrence of side effects, and drug resistance. Therefore, there is a pressing need to discover more effective and efficient approaches and drugs for treating CRC. This chapter will shed more light on the conventional treatment of colorectal cancer. This chapter discusses the natural products that have anti-CRC effects such as the polyphenols (curcumin, resveratrol), irinotecan, Ganoderma lucidum, cannabinoids, flavonoids, and terpenes. Furthermore, this chapter also highlights the importance of combination chemotherapy (conventional therapy and natural products) in treating CRC. It is believed that this area of research could be a promising approach to minimize side effects and drug resistance linked to the conventional chemotherapy.

cancer involves radiotherapy or chemotherapy, which alters the physical condition of the individual with diverse side effects and ultimately drains the immunity of the individual. Several available drugs are also unable to cure cancer completely, but recent advancement in utilization of plant-based compounds revealed greater beneficial efficacy in management of cancerous cell growth. Therefore, this chapter portrays the bioactive compounds obtained from natural sources and how these traditional medicines act as drug candidates against cancer.

The occurrence of tumor cells is generally governed by the cluster of cells known as cancer stem cells, which are based on the informative model of cancer tissue consisting of stem cells that do have characteristics like auto-renewal activity and also provide intrinsic mechanisms for survival which are responsible for resistance against tumor cells to most of the drugs used in chemotherapy to cure cancer. During the course of therapy, it is difficult to eliminate CSCs due to which recurrence of tumor and metastasis develops inside the cell. Ongoing studies provide significant information on the particular phenotypic characteristics of cancer stem cells from different tumor types, as well as the signaling system and molecules that undergo auto-renewal and drug resistance. NPs (natural products), which are derivative of botanicals and food sources, may alter important signalling pathways that are involved in the perpetuation of CSC phenotypic traits. The chapter deals with the use of plant products to cure CSCs and their functioning.

Cancer is the second world's deadliest disease. Despite substantial advancements in medical technology for cancer therapies, cancer mortality remains greater than projected, and cancer treatment requires additional study. The research carried out in natural products is due to the presence of bioactive compounds, unique structures, and mechanistic actions. Prevention of drug resistance in chemotherapy is predominant in the usage of anticancer drugs. Clinical chemotherapeutic medicines work by causing cancer cells to die, the majority of which is apoptotic. Another way to combat drug resistance in cancer therapy is circumventing apoptosis by targeting non-apoptotic cell death. The authors discussed in this chapter both apoptotic and non-apoptotic cell death.

Breast cancer (BC) is the most prevalent malignancy in women. The main treatment for BC is surgery and chemotherapy. Generally, the chemotherapeutic drugs used for treatment cause numerous side effects. Substances derived from natural products have proven to exhibit anti-cancer effects without causing side effects. For instance, biochannin A found in cabbage and cauliflower reduced the growth of estrogen dependent MCF 7 cells. Another example is curcumin present in turmeric exhibits anti-proliferative and inhibitory effect against BC. The active compound of Nigella sativa is thymoquinone. The oil extracted from Nigella sativa reduced blood pressure. Nigella sativa exerts anti-pyritic, anti-inflammatory, and anti-microbial activity. Thymoquinone is found in seeds of Nigella sativa. Thymoquinone is a promising anti-neoplastic, anti-carcinogenic, anti-proliferative agent. In this chapter, the authors emphasize the anticancer potential of Nigella sativa and its derivatives and the mechanism of action against BC.

Section 2
Active Ingredients of Natural Products as Cancer Therapeutics

Flavonoids, defined as plant-derived secondary metabolites, have been widely found in nature with more than 10,000 different species, since their discovery. They are divided into subclasses based on the oxidative state of the ring, such as flavones, flavonols, flavanones, isoflavones, flavandiols, dihydroflavonols, and anthocyanidins. They are promising compounds with a wide variety of biological activities including antioxidant, antitumor, antigen-toxicity properties. Furthermore, flavonoids are seen as promising tools in the development of new drug assets, and they have been the subject of studies for the development of high-efficiency formulations for the treatment of a variety of future-threatening diseases. Molecular modeling studies play an important role in identifying the most stable molecular configurations and conformations of these molecules. This chapter focuses on the structural and functional properties of flavonoids, their biological activities, bioavailability, use in cancer, use in the development of new drugs, and molecular modeling studies on these molecules.

Flavonoids are a group of over 2000 phenolic compounds with many therapeutic properties. They are based on the flavan (2-phenyl-benzopyran) core and can be found in a free state or as glycosides. Flavonoids are presented in the vegetal world mainly as yellow, but also red, purple, blue, or brown pigments of the petals, leaves, stems, and fruits. This group of bioactive compounds is known for the inhibition of tumors. The chapter summarizes the most important flavonoids with anti-cancer properties, describing their chemical structure, their prevalence among medicinal plants, and their mechanism of action, based on the recent in vivo and in vitro studies.

Section 3
Antioxidant Natural Products as Cancer Therapeutics

The purpose of this chapter is to reveal the important properties of some anticancer antioxidants. Cancer can be defined as a disease caused by very different cell types and organs of the human body and characterized by very fast growth and the ability to metastasize to other organs. Cancer cells typically exhibit higher levels of basal ROS than normal cells, mainly due to their increased metabolism, oncogene activation, and mitochondrial dysfunction. Antioxidant system is a form of defense against high ROS production in cells. Quercetin plays an important role in the prevention and treatment of many types of cancers. Resveratrol is considered a potential candidate for the prevention and treatment of many types of cancer. Antioxidants such as CAPE, Quercetin Resveratrol, which have antioxidant properties and destroy ROS, may be a promising treatment strategy in cancer. Antioxidants are thought of as popular natural remedies that are used by the majority of people and have few side effects. However, even with the available data, more experimental and clinical studies are needed.

The inequality between the production of free radicals and reactive oxygen species, and their elimination by protective mechanisms, is defined as oxidative stress, which destroys cell components by creating various forms of free radicals that influence the pathogenesis of many diseases, such as cancer. Natural preservatives such as phytochemicals inhibit the production of free radicals and maintain oxidative balance. Lycopene, which has the high antioxidant ability, is one of these phytochemicals that reduces oxidative stress markers. Studies show a connection between a lycopene-rich diet in the prevention of oxidative stress harm. Lycopene is believed to minimize the risk of cardiovascular disease, cancer, metabolic syndrome, and obesity. In this chapter, the biochemical, structural, chemical, biological, and oxidative stress mechanisms of lycopene are evaluated, and the role of lycopene on cancer is discussed.

Section 4
Novel Approaches of Natural Agents as Cancer Therapeutics

Breast cancer is the most common malignant disease in women worldwide. Despite much technological progress, the current clinical therapy's lack of specificity leads to reduced therapeutic efficiency and serious systemic side effects. In recent years, nanotechnology applications for cancer treatments have attracted a lot of attention because of their advantages in tumor targeting, prolonged blood circulation time, and enhanced accumulation of drugs in tumors. Many liposomal and polymeric-based formulations have been developed to treat breast cancer and showed significantly higher efficiency than free drugs in clinical trials. The versatility of nanoparticles allows for the delivery of multiple active agents with the ability to target various types of cancer. Nanotechnology is a promising field that is expected to introduce new strategies to positively impact the survival rates and quality of life of breast cancer patients. This chapter presents the advantages and disadvantages of nanotechnology applications in breast cancer.

Plant-based natural products provide a strong background to evaluate, predict the novel class of compounds having anti-cancer properties, as well as to explore their potential mechanism mechanisms of action. Due to the huge cost and time utilization in the traditional drug development approaches, bioinformatics plays a major role to facilitate drug discovery with less cost and time strategies. Several bioinformatics-based approaches being used recently to screen as well as to characterize the potential plant-based compounds can be used to treat several types of cancer. Some of the computational approaches are target identification, screening of compounds molecular docking, molecular dynamics simulations, QSAR analysis, pharmacophore modeling, and ADMET (absorption, distribution, metabolism, excretion, and toxicity). This chapter describes specific computational methods being used currently to screen and characterize different plant-based anti-cancer molecules by taking examples from the recent literature and discussing their advantages and limitations.

Preface

Cells are the structural and functional unit of the human body. Cells grow and multiply through cell division when cells become old or get damaged in a normal condition. In certain circumstances, this process of cell division is disturbed, leading to abnormal or damaged cells growth. These cells that grow uncontrollably and spread to other body parts are called tumors (lumps of tissue), leading to cancer. The tumors can be cancerous or non-cancerous. When cancerous tumors spread to the nearby cells or tissues, they can even travel to various parts of the body that are very distant. This process is called metastasis. However, when the cells don't spread to any parts of the body, they instead grow uncontrollably at a single site leading to solid tumors is the malignant tumors. At the same time, benign tumors (non-cancerous) don't invade nearby cells or spread. Sometimes these tumors can be life-threatening based on the site affected, like tumors in the brain. When the benign tumors are removed from the body through surgery, they usually don't grow back, but cancerous tumors spread even after surgery. Normal cells grow when they receive signals, and they don't invade spread to other parts of the body, but the cancer cells grow without any response from the signalling system. And also, cancer cells ignore the apoptosis process (programmed cell death), hide from the immune system, influence various changes in the chromosomes (deletion, insertion, or duplications), and utilize more nutrients than the normal cells.

Cancer is a genetic disorder that is caused due to the changes in genes that control the functions of cells (cells growth and multiplication). Genetic changes that lead to cancer include DNA damage by exposure to Ultraviolet rays, genetic inheritance from the parents, and errors during cell division. Generally, the human body's immune system eliminates the damaged DNA before turning cancerous. But the cancerous cells hide from the immune system, or the body's ability to determine the defective DNA goes down as age increases. This is the reason why aged people are more prone to cancer. Three main types of genes responsible for genetic changes in cancer are proto-oncogenes, tumor suppressor genes, and DNA repair genes. Proto-oncogenes are usually involved in average cell growth. Still, these genes get altered or become more active than normal, leading to cancer-causing genes allowing the cells to grow and multiply when necessary. Tumor suppressor genes are involved in regulating cell growth and division. Alteration in the tumor suppressor genes leads to an uncontrolled manner. DNA repair genes mainly focus on fixing the DNA damage. Cells with the mutations lead to multiple mutations in nearby genes, leading to chromosome duplication and deletion. Together all these genetic changes lead to cancer. The current treatment methods are include surgery, radiotherapy and chemotherapy. Chemotherapeutic drugs effective against cancer cells but due to the serious side effects.

Nature provides an abundant source of diverse biological molecules. Only few natural products have been identified, isolated, and developed into commercial product that plays a significant role in cancer therapy. Apart from cancer therapy, natural products possess variety of beneficial effects including anti-

diabetic, antioxidant, cardioptective, hepatoprotective, antidepressant, neuproportective, nephroprotective and antiproliferative property. This area of research provides strong evidence for identifying biologically active compounds with novel mechanisms of action and unique structures. Plant compounds possessing anti-tumour activity generally belongs to alkaloids, anthracyclines, isoprenoids, polyketides, peptides, enediynes. Taxol, camptothecin and vinblastine, phytochemicals like sulforaophane, phenethyl isothiocyanate, and resveratrol are natural products used in cancer treatment. They act by various mechanisms like apoptosis, DNA cleavage by topoisomerase I, inhibition of key enzymes involved in signal transduction, inhibiting tumor induced angiogenesis.

Vinblastine, commonly used to treat cancers like lymphoma is obtained from *Catharanthus roseus*. The compounds are eco-friendly with the anti-tumor property. The plant Nathapodytes foetida produces Camptotechin was used to treat colon cancer and is also reported to possess activity against ovarian, uterine and lung cancer. Commercially it is marketed as Camptosar and Campto. Taxol, a diterpene alkaloid is a very prominent anti-tumor molecule. It is isolated initially from *P. citricarpa, Taxomyces adranae*. Taxol is approved for the treatment of ovarian and breast cancer. It reached a sale of 1.6 billion dollars in 2005. An analogue of taxol, docetaxel, sold 3 billion dollars in 2009. It also possesses antifungal properties.

The shikonin (naphthoquinone pigment) a herbal medicine produced by the plant *Lithospermum erythrorhizon,* is studied for its anti-tumor activity in lung cancer mice. Genistine, indole-3-carbinol, curcumin, and lycopene also inhibit cancer cells. They act through multiple cellular signaling pathways, cell death by bringing on apoptosis without causing damage to the normal cells.

From ancient days, podophyllotoxins are used in the treatment of skin cancer. It reversibly binds to tubulin, etoposide and teniposide; the active compounds of podophyllotoxins induces DNA cleavage by inhibiting topoisomerase II. Paclitaxel obtained from Taxus breyifolia is used in the traditional medicine system for treating cancer. They promote the polymerization of tubulin heterodimers and suppress the microtubule's dynamic changes resulting in mitotic arrest, thus controlling the multiplication of the cancer cells. This bioactive molecule is isolated from the ornamental tree of china *Camptotheca acuminata*. It acts by binding to the topoisomerase I – DNA resulting in a stable ternary complex, thus preventing DNA relegation and causing DNA damage resulting in apoptosis.

The FDA approves this drug to treat thyroid cancer, medullary cancer, follicular thyroid cancer. When treated along with paclitaxel/ carboplatin, this drug is proven to be more effective in treating ovarian cancer. High throughput screening, combinatorial chemistry should aid in providing more insights in identifying the anti-tumor compounds. Combinatorial chemistry yields minor modifications of the present-day drugs and requires more information on natural products and on which to build. The pharmaceutical industry's success depends on both high throughput screening and combinatorial chemistry for genuine product discovery, proteomics, metagenomics, metabolomics and structure-function drug design, recombinant DNA methodology. All these together could provide exciting technologies for the new natural product-based drug delivery and the tremendous development of anti-tumor compounds.

Luteolin is a flavonoid that attenuates cognitive dysfunction induced by chronic cerebral hypoperfusion through the modulation of The PI3K/Akt Pathway in rats. It possess anutitumor activity against colorectal cancer by modulating the Wnt/β-catenin signaling. Luteolin induces apoptosis by inducing the Bax, caspase 3 and downregulating Bcl2. Luteolin Confers Cerebroprotection after Subarachnoid Hemorrhage by Suppression of NLPR3 Inflammasome Activation through Nrf2-Dependent Pathway. Vernodalin is a Sesquiterapene compound that showed antidiabetic activity in Sterptozotocin induced diabatetes in rats. It also showed to induce apoptosis in breast cancer cells. In addition, it modulates the

FOXO signlaing to suppress the tumor in MCF-7 cells and in Rat model. In this book comprised of 21 chapters and each chapter have unique information about natural products as cancer therapeutics.

Chapter 1 depicts about the bout the treatment opportunities and highlights the importance of few oncogenic transcription factors which may act as an important biomarker specifically for Triple Negative Breast cancer (TNBC).

Chapter 2 depicts about the chemopreventative and anti-cancer activities of different bioactive compounds obtained from dietary sources, herbal approach and use of natural compounds such as diindolylmethane, biochanin A, curcumin, Epigallocatechin Gallate, genistein, lycopene, shikonin, sulforaphane and resveratol. Understanding the pathophysiology of action of these compounds and their potential preventive and therapeutic effects on cancer.

Chapter 3 depicts the summarization of 12 well known natural products such as chebulinic acid, maslinic acid, apigenin, piperlongumine, Liquiritigenin, berberine, icariin, bufalin which are targeted against TNBC through regulation of different pathways and their mechanism is briefly explained. These, natural products are already used to treat various diseases at the preclinical level and also has shown to have effective anti-tumor effect and can act as potent anti TNBC agent.

Chapter 4 depicts the natural products that have anti-colorectal cancer effects such as the polyphenols (curcumin, resveratrol), irinotecan, Ganoderma lucidum, cannabinoids, flavonoids and terpenes. Furthermore, this chapter also highlights the importance of combination chemotherapy (conventional therapy and natural products) in treating colorectal cancer. It is believed that this area of research could be a promising approach to minimize side effects and drug resistance linked to the conventional chemotherapy.

Chpater 5 depicts the ole of the gut microbiome and modification of the gut microbiota to improve treatment efficacy and minimize adverse effects of colorectal cancer therapies. Natural candidates like gut microbes and plant-derived bioactive components demonstrate their efficacy in appropriate in vivo models and clinical studies, which may lead to the discovery of alternative therapy for colorectal cancer.

Chapter 6 depicts to display anti-colorectal cancer effects of natural products based on chemical structure such as alkaloids, terpenoids, polysaccharides, polyphenols and unsaturated fatty acids. Furthermore, drugs derived from natural products used clinically for the treatment of colorectal cancer are discussed. This work also highlights natural products with marine origin as a candidate drugs for colorectal cancer. This work highlights the importance of natural products as promising sources of lead anti-colorectal medicine.

Chapter 7 depicts the bioactive compounds obtained from natural sources and how these traditional medicines acts as drug candidates against the devastating cancer disease worldwide.

Chapter 8 depicts the use of plant products to cure Cancer Stem Cells (CSC) and their functioning. During the course of therapy, it is difficult to eliminate CSCs due to which recurrence of tumor and metastasis develops inside the cell. On-going studies provide significant information on the particular phenotypic characteristics of cancer stem cells from different tumor types, as well as the signaling system and molecules that undergo auto-renewal and drug resistance. Natural products), which are derivative of botanicals and food sources, may alter important signalling pathways that are involved in the perpetuation of CSC phenotypic traits.

Chapter 9 depicts the research carried out in natural products is due to the presence of bioactive compounds, unique structures, and mechanistic actions. Prevention of drug resistance in chemotherapy is predominant in the usage of anticancer drugs. Clinical chemotherapeutic medicines work by causing cancer cells to die, the majority of which is apoptotic. Another way to combat drug resistance in cancer therapy is circumventing apoptosis by targeting non-apoptotic cell death.

Chapter 10 depicts the brief insight about the various marine fungal metabolites (Alterporriol L and Scopararane I) with potential anticancer activity against cervical and breast cancer and evidences it as a promising source of anticancer therapeutics.

Chapter 11 depicts diverse medicinal plants and their bioactive compounds that used in therapeutic and management intervention against liver cancer.

Chapter 12 depicts to emphasize the anticancer potential of Nigella sativa and its derivative Thymoquinone and the mechanism of action against breast cancer.

Chapter 13 depicts the structural and functional properties of flavonoids, their biological activities, bioavailability, use in cancer, use in the development of new drugs, and molecular modeling studies on these molecules.

Chapter 14 summarize the most important flavonoids with anti-cancer properties, describing their chemical structure, their prevalence among medicinal plants, and their mechanism of action, based on the recent *in vivo* and *in vitro* studies.

Chapter 15 depicts that the flavonoids can be used as a potential anti-cancer natural compound that not only achieve anti-cancer efficacy but also improve the survival and life expectancy of cancer patients.

Chapter 16 depicts the critical assessment of naturally occurring alkaloids with anticancer properties, and an overview of some of the alkaloid-containing natural compounds that have demonstrated significant anti-proliferative activity and progressed to preclinical and/or clinical trials in the context of future drug development for cancer therapy.

Chapter 17 depicts that the Lectins are powerful oral and parental immunogens and some of their physiological effects are intricately linked to interference with immune function. Lectins are produced by wide range of living organisms from microbes to mammals. They function as both allergens and heamagglutinins. The chapter summarizes that the Lectins as an therapeutic agent against cancer.

Chapter 18 depicts that the cancer cells typically exhibit higher levels of basal ROS than normal cells, mainly due to their increased metabolism, oncogene activation, and mitochondrial dysfunction. Antioxidant system is a form of defense against high ROS production in cells. The chapter summarizes the CAPE, Quercetin Resveratrol, which have antioxidant properties and destroy ROS, may be a promising treatment strategy in cancer.

Chapter 19 depicts that the Lycopene is believed to minimize the risk of cardiovascular disease, cancer, metabolic syndrome, and obesity. In this chapter, the biochemical, structural, chemical, biological, and oxidative stress mechanisms of lycopene are evaluated and the role of lycopene on cancer is discussed.

Chapter 20 depicts that the Nanotechnology is a promising field that is expected to be new strategies to positively impact the survival rates and quality of life of breast cancer patients. This chapter presents the advantages and disadvantages of nanotechnology applications in breast cancer.

Chapter 21 describes specific computational methods is being used currently to screen and characterize different plant-based anti-cancer molecules by taking examples from the recent literature and discussing their advantage and limitations.

In this book, we documented the natural products and their derivates on various cancers in detail. This book will cover the audience of undergraduate, postgraduate, research scholars, scientists and faculty members, and medical practioners.

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Section 1

Natural Products as Cancer Therapeutics

Chapter 1
An Update on the Effect of Natural Products on Oncogenic Transcription Factors in Triple Negative Breast Cancer

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ABSTRACT

Breast cancer is the most aggressive and rapidly growing cancer worldwide. It is classified into several subtypes among which triple negative breast cancer (TNBC) is the most aggressive. Oncogene regulation leads to increased signal activity in the cells and contributes to the tumorigenic phenotype. Such signals generate a large number of proteins that provoke cell growth and inhibit cell death. Transcription factors, such as miR-27a, NF-κB, and FOXM1, are proteins that are conserved across species, abundantly found in the nucleus, bind to DNA, and enforce specific target genes. Oncogenic transcription factors arising from mutation accompanying aberrant gene expression transfer signals to the nucleus and interrupts transcription patterns and stimulation of oncogenic transcription factors consistent with cell cycle regulation, apoptosis, proliferation, and cell differentiation. This review gives a detailed framework about the treatment opportunities and highlights the importance of few transcription factors which may act as an important biomarker specifically for TNBC.

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INTRODUCTION

Breast cancer (BC) is a malignant tumor that occurs in the breast cells. This starts in the breast tissues and travels primarily across the lymphatic system. It is reported mostly in women. BC is a type of cancer in which breast cells proliferate and grow out of control (Corso *et al.,* 2020). The type of BC relies on which breast cells transform into cancer. BC is one of the highly prevalent malignancies and one of the top ten cancers worldwide (Ferlay *et al.,* 2010).

Generally, BC may start in various sections of the breast. The breast consists of three primary parts: lobules, ducts and connective tissue. Lobule, where glands produce milk, ducts are tubes that deliver the milk to the nipple and the connective tissue (which is made up of fibrous and fatty tissue) covers and binds all of this together (Woolas et al., 2020). The majority of BCs begin in the ducts or lobules. BC cells spread outside the breast through blood and lymphatic vessels. If BC progresses to other areas of the body, it is said that it has metastasized (Pandurangan and Mustafa, 2018; To et al., 2020).

Based on recent reports the survival rate of BC is given to be (Lerebours and Lidereau, 2002):

- Stage 0 – 100%
- Stage I - 100%
- Stage II – 93%
- Stage III – 72%
- Stage IV - 22%

BC is initially classified into 2 groups - malignant which is non-cancerous and benign which is highly dangerous and cancerous [Miller *et al.,* 2019). Further BC is divided into several types:

- Invasive Ductal Carcinoma.
- Invasive Lobular Carcinoma.
- Ductal Carcinoma in situ (DCIS)
- Lobular Carcinoma in situ (LCIS)
- Inflammatory Breast Cancer (IBC)
- Metastatic Breast Cancer (MBC)
- Triple Negative Breast Cancer (TNBC)

Breast Cancer Effects

When BC is metastasized, it affects several other regions or organs of the body. Few among the drastic effects of BC which is organ system specific are as follows:

i. Integumentary (skin) system:

In addition to the breast changes by themselves, BC can also affect the skin around the breast. It might be extremely itchy and could become dry and cracked. Many women often report dimpling of skin over their breasts, which appears like orange peel drops. Breast tissue thickening is also common in BC patients [Waks and Winer, 2019).

ii. Immune and Excretory Systems:

During the later stages of BC, tumor spreads to the lymph nodes. Arm pits are some of the first areas to be affected. It is because of their close proximity to the breasts. Tumors metastasize through the lymphatic system to the lungs and the liver (Foulkes *et al.,* 2010; Waks and Winer, 2019).

Nervous system:

BC can also spread to the brain eventually acting as the host to various neurological effects, including:

- blurry or double vision
- seizures
- mobility issues
- memory loss
- speech difficulties

However, in this review, TNBC, its treatment and the various oncogenic transcription factors related to it are further detailed and discussed. In addition, we listed out few natural agents that target the transcription factor that is dysregulated in TNBC.

Triple Negative Breast Cancer (TNBC)

TNBC is characterized by tumors that do not express receptor of estrogen (ER), progesterone receptor (PR) and the human epidermal growth factor receptor (HER)-2 genes. In contrast to the hormone receptor positive and ERBB2+ BCs, TNBC is a form of cancer with biological aggressiveness, poor prognosis and lacks potential therapy (Pandurangan and Mustafa, 2018). Certain important feature of TNBC is mentioned in Table 1. Latest approaches demonstrate that TNBC have a clinical path more severe than other types of BC, but the adverse effect is ephemeral (Foulkes *et al.,* 2010).

TNBC is very often said to be similar to the sub group of Basal like BC which can better be defined through microarray gene-expression data analysis (Sørlie *et al.,* 2001). This subtype encompasses a heterogeneous group of tumors characterized by lack of or low levels of estrogen receptor expression, very low HER2 prevalence which is typically found in basal or myoepithelial cells of the breast. There is still no internationally accepted definition for these tumors owing to the reason that a majority of basal-like cancers are also triple-negative and also a majority of TNBCs (approximately 80%) are also basal-like BCs (Foulkes *et al.,* 2010); Weigelt *et al.,* 2010). Hence, triple-negative and basal-like BCs are remarkably heterogeneous at the genetic level. Amplification of various genetic regions has been reported, however, the ubiquity of each of these amplified regions is low (Paroni *et al.,* 2020).

TNBC is a significant clinical concern as this type of cancer does not respond to endocrine therapy or therapies directed at the human type 2 epidermal growth factor receptor (HER2) and other selective agents. In TNBC, the risk of metastasis is similar to any other BC subtypes (Foulkes *et al.,* 2010). However, TNBC is correlated with a low relapse time and its early visceral metastases is attributed as the chief cause of death in patients. Recent researches show that cumulative incidence curves are representative of recurrence rates. In order to assess more precisely the timing of recurrence for both the subgroups, the annual risk rate of distant recurrence was estimated at 6-month intervals (Dent *et al.,* 2007). In patients

Table 1. Certain important characteristic features of TNBC

Characteristic Features	TNBC
Histological Type	Ductual Carcinoma
Resemblance	Basal like Breast Cancer
Histological grade	More often Grade III, sometimes Grade II
Metastatic Potential	Sporadic
Prognosis	Intermediate in first 5 years
Relapse	Rare after 10 years of diagnosis
Gene Expression Profile	More often Basal like, sometimes claudin type
Estrogen Receptor	Negative
Progesterone Receptor	Negative
HER-2 gene	Negative
Cyclin E	Frequently Positive
CK5 or CK17	Frequently Positive
Hormone or Endocrine Therapy	Not Possible
Chemotherapy treatment	Possible but there is no concord
Other known effective agents	Platinum salts, PARP inhibitor, Antiangiogenic agents.

with TNBC, the risk of recurrence increased sharply from the date of diagnosis, peaked at 1 to 3 years, and decreased rapidly thereafter. On the other hand, in patients with several other cancers, there seemed to be a steady risk of recurrence over the entire period (Dent *et al.,* 2007; Collett *et al.,* 2005). Based on the statistical analysis, the mean age of diagnosis was significantly younger for the triple-negative group when compared to other BC groups. Patients with TNBC were highly probable to have grade III tumors and the mean tumor size seemed to be significantly bigger in the triple-negative group than in the other sub-types (Livasy *et al.,* 2006). Women with TNBC were more likely to die within 5 years of diagnosis. After adaptation for age, tumor size, grade, nodal status, tamoxifen therapy and chemotherapy, the risk of BC death remained higher for the TNBC group up to 5 years after detection (Dent *et al.,* 2007). Ideal therapeutic approach for TNBC is likely to include a combination of targeting the host through an accurate knowledge of pharmacogenetics and cancer oriented molecular biology like the transcription factors. Relying on the attempts to couple molecular biology of TNBC along with drug mechanism, numerous compounds have been tested. These include polymerase inhibitors (ADPribose), taxanes, antiangiogenic agents, EGFR inhibitors, platinating agents and Src-Abl inhibitors and also various transcription factors (Sitterding *et al.,* 2008).

Current Approaches for TNBC Treatment and their Difficulties

Chemotherapy is still the primary treatment for TNBC till date. Recent finding reflects the intrinsically adverse prognosis associated with the disease. TNBC patients do not benefit from endocrine or trastuzumab therapy, and have an even worse outcome after chemotherapy than patients with BCs of several other subtypes (Carey *et al.,* 2006).

Currently available treatments include a number of chemotherapeutic agents, such as ixabepilone, anthracyclines, taxanes, platinum agents, as well as selected biological agents like anti-EGFR drugs. It has already been demonstrated that regimes based on anthracyclines and taxanes such as taxan-fluorouracil-doxorubicin-cyclophosphamide (T-FAC) protocol is used in MD Anderson studies. Similarly, doxorubicin-cyclophosphamide-taxane used in the National Surgical Adjuvant Breast and Bowel Project (NSABP) studies demonstrated significantly higher response rates in TNBC patients (Kim *et al.,* 2009). Even with this elevated response rate, this subgroup has a much shorter disease-free survival and overall survival rate. Researchers these days have focused on enhancing the drug selection of existing chemotherapeutic agents. From a biological perspective, DNA-damaging agents (such as platinating agents) are of high importance on the basis of the BRCA 1 pathway as they accomplish DNA repair dysfunction, thereby proving increased susceptibility rates of the DNA-damaging agents (Rouzier *et al.,* 2005). As per recent research, Neoadjuvant studies involving pre-operative chemotherapy suggests that this treatment is very effective in TNBC patients who exhibit complete pathological response and therefore an outstanding outcome is observed. However, on the other hand, the outcome for majority of women who still have residual disease after treatment is relatively poor.

Strategies to Battle TNBC

An optimal therapeutic approach for TNBC requires a combination of detailed understanding of the pharmacogenetics of the host and targeting the molecular biology of the tumor, especially focusing on the various transcription factors involved. Based on this concept, several drugs have been tested against TNBC [Carey *et al*., 2007). CALGB 40603 is a neoadjuvant trial primarily tailored for people with TNBC that tackles two very important concerns (Hayes *et al.,* 2007). It involves the incorporation of a platinating agent or an antiangiogenic treatment or both being applied along with the conventional chemotherapy. The role of EGFR in basal-like BC continues to be another pivotal aspect in focus. Vascular endothelial growth factor receptor-2 small-molecule tyrosine kinase inhibitor sunitinib has been studied in advanced settings where patients are randomly selected to sunitinib versus standard treatments. Certain novel agents of interest include the multi-target dasatinib of Src-Abl inhibitor (Carey *et al*., 2007). Polymerases (ADP-ribose) are molecules that are crucially involved in non-homologous DNA repair. They are also the main means of double-strand DNA repair when the desired homologous recombination process is damaged, which tends to happen when the BRCA1 pathway is faulty. Hereditary and a minimum subset of intermittent basal-like BC is believed to have defective BRCA1 pathways. This leads to multiple phase II trials of poly (ADP-ribose) polymerase inhibitors alone and in tandem with DNA modifying agents for both BRCA1 carriers and TNBC. In addition to the choice of medications based on an intuitive knowledge of the molecular biology of TNBC, the production of companion predictive markers will potentially maximize clinical effectiveness (Arslan *et al.,* 2009).

Some of the chemotherapeutic and biological agents that seem most promising for their implications in TNBC treatment are as follows:

Platinum Derived Compounds

Platinum compounds induce their effects by forming covalent, bi-functional, inter-and intra-strand, cross-linked adducts. Covalent binding to other subcellular components also occurs, including proteins, lipids, RNA and mitochondrial DNA. However, the scientific consensus is that the primary mode of

cell killing is cell DNA destruction. Inter-strand cross-links induced by platinum compounds as well as other bi-functional alkylating agents present a significant block to replication forks leading to DNA double-strand breaks and replication lesions. DNA-damaging agents, such as platinating agents, are of great concern as a therapeutic alternative for TNBC based on the BRCA1 pathway and DNA repair dysfunction (DeVita *et al.,* 2005). The reasonable use of platinum compounds in the treatment of TNBC depends on the outcomes of BRCA1-defective tumors.

Antiangiogenic Therapy

Angiogenesis is a main mechanism for tumor development. The advancement of drugs that target cellular pathways engaged in neoangiogenesis is currently one of the research priorities. Targeting and inhibiting the formation of blood vessels disrupts the environment that the tumor cells create in order to receive the oxygen and nutrients needed for survival and maintain connection with each other. In vitro experiments indicate that vessels formed in the tumor settings are unstable and have altered morphology, which in turn makes it impossible for cytotoxic therapy to reach the tumor and facilitates trans-endothelial migration of tumor cells that causes metastases (Vidula *et al.,* 2020).

Bevacizumab

Bevacizumab is a humanized monoclonal anti-vescular endothelial growth factor antibody. The clinical role of bevacizumab is troublesome for all BCs types and not better for TNBC either. Across all prospective clinical trials identified for bevacizumab, there is no clear evidence that this anti-angiogenic agent has any unique properties in treating TNBC (O'Shaughnessy *et al.,* 2009).

EGFR Antagonists

Expression of the Epidermal Growth Factor Receptor (EGFR) is seen in approximately 45–70% of TNBC [Hynes and Lane, 2005). The suppression of this target is also used as a therapeutic strategy. Cetuximab (Merck Serono), a chimeric monoclonal antibody against EGFR, is now being tested in a metastatic TNBC setting. In a recent approach, two findings of the phase II trials upon treatment with cetuximab were presented. In the first study, 74 BC patients randomly received irinotecan and carboplatin (ICb) with or without cetuximab. This research indicated a slightly greater response of around 49% for a type of TNBC. In the second study, patients with TNBC were randomly assigned to receive either cetuximab in monotherapy or in combination with carboplatin. Many other clinical trials are currently evaluating the effectiveness the monoclonal antibody (cetuximab) and also a tyrosine kinase inhibitor. Unfortunately, this form of procedure is currently under review only (Carey *et al*., 2012).

POLY (ADP-RIBOSE) POLYMERASE INHIBITORS (PARP)

PARP inhibitor signals the presence of DNA damage and facilitates the repair of DNA by base excision repair. Inhibition of PARP during the cell cycle S-phase causes DNA single-strand breaks which result in the arrest of the replication fork leading to DNA double-strand breaks. These lesions are usually repaired by HR but, in the absence of functional BRCA1 or BRCA2, this mechanism is impaired and the faults

may be corrected by error-prone mechanisms such as non-homologous end-joining and single-strand annealing (Bryant *et al.,* 2005). These changes will cause complex chromatid re-arrangements, resulting in cell cycle arrest at the G2 / M cell cycle checkpoint and apoptosis thereafter. Recent studies in mouse models (*In vivo*) suggest that the accuracy of platinum compounds with PARP1 inhibitors helps to improve treatment response. It also induces the prolonged recurrence of free survival and overall survival rates. Data from pre-clinical and clinical trials show that PARP inhibitors have anti-tumor effects where one of the pathways for tumor growth is a faulty DNA-repair mechanism. In addition, PARP inhibitors also help in promoting the treatment response when combined with classical chemotherapeutic agents that induce DNA damage (Bernstein *et al.,* 2002).

Androgen Receptor Targeted Therapy

Recent research focuses on the Androgen Receptor (AR). Cluster analysis of 99 specimens through a tissue microarray (TMA) was performed and the investigation revealed that there were a number of additional genes that were up-regulated which were similar to those seen in the ER-positive BC cases (Doane *et al.,* 2006). Downstream expression analysis conducted on ER and PR negative tumors reported that they were similar to the ER positive subtype. Besides, these patients also exhibited AR as opposed to ER. However, the challenge with the use of targeted AR drugs is that if TNBC cases represents 20% of the disease population and if 10% of that is positive for AR, then this represents only 2% of the total cases of the BC population (Barton VN *etal.,* 2015; Doane *et al.,* 2006).

Neoadjuvant Treatments for TNBC

Neoadjuvant chemotherapy facilitates improvement in future treatment and also aids in combination treatments. Neoadjuvant therapy strategy has in general a very high pathological response rate against TNBC than the other forms of BCs. However, more than half of the TNBC patients don't really have a complete pathological response and display very poor prognosis (Di Leo *et al.,* 2011). The lack of drug targeting receptors for TNBC has made the improvement of the available interventions a significant medical need. The regular use of neoadjuvant anthracycline / taxane combinations in TNBC is currently complemented by current investigations along-side their use with other types of agents. Neoadjuvant treatment identifies therapeutic intervention prior to surgery (Sikov *et al.,* 2010). The objective of neoadjuvant therapy in BC was primarily focused to limit the size of unresectable tumors, thereby enabling surgery. In addition, neoadjuvant therapy in surgical removal of tumors allows greater breast retention and reduced need for mastectomy. Currently, anthracycline / taxane chemotherapy regimens have been regularly used in the neoadjuvant setup in TNBC treatment. Clinical trials of many novel targeted neoadjuvant therapies for TNBC are currently underway (Martin *et al.,* 2010).

Role of Transcription Factor in BC

Transcription factors are proteins associated with the process of transcribing DNA into RNA that further promote gene expression. Transcription factors include a large number of proteins, except for RNA polymerase, which initiate and regulate gene transcription. A unique aspect of transcription factors is that they have DNA-binding domains that give them the ability to bind to specific DNA sequences called promoter sequences (Thiery *et al.,* 2009). Certain transcription factors bind to the DNA promoter sequence

near the transcription start site and help form the transcription initiation complex. Transcription factors also bind to regulatory sequences, like the enhancer sequences, and either promotes or suppresses the transcription of the relevant gene. These regulatory sequences may be thousands of base pairs upstream or downstream of the gene being transcribed. Regulation of transcription is the most important form of gene control (Iorio *et al.,* 2012).

Oncogenic transcription factors are gene expression promoters and their activity contributes one way or the other to tumorigenesis. They are generally classified into three classes in the BCs: steroid receptors, latent cytoplasmic factors and resident nuclear transcription factors (Pandurangan and Mustafa, 2018). The over-activity of these oncogenic transcription factors helps in the survival of BC cells. The molecular signaling pathways influence these oncogenes, and have diverse associations with each other as well. As a result, diagnosis and clinical outcomes are getting delayed. Subsequently through time, learning about oncogenes, their proteins and their functions may lead to more selective and more effective treatment regimens (Osborne et al., 2005).

Oncogenic transcription factors arising from mutation or overexpression owing to gene expression, transfer signals to the nucleus and interrupt the transcription sequence. Activation of oncogenic transcription factors is consistent with cell cycle regulation, apoptosis, proliferation and cell differentiation (Iorio *et al.,* 2012). Oncogenic transcription factor is reported to be essential in BC carcinogenesis and therefore is considered a potential target for BC therapeutic strategies. Certain key Oncogenic Transcription Factors and their regulation in particular to TNBC are discussed.

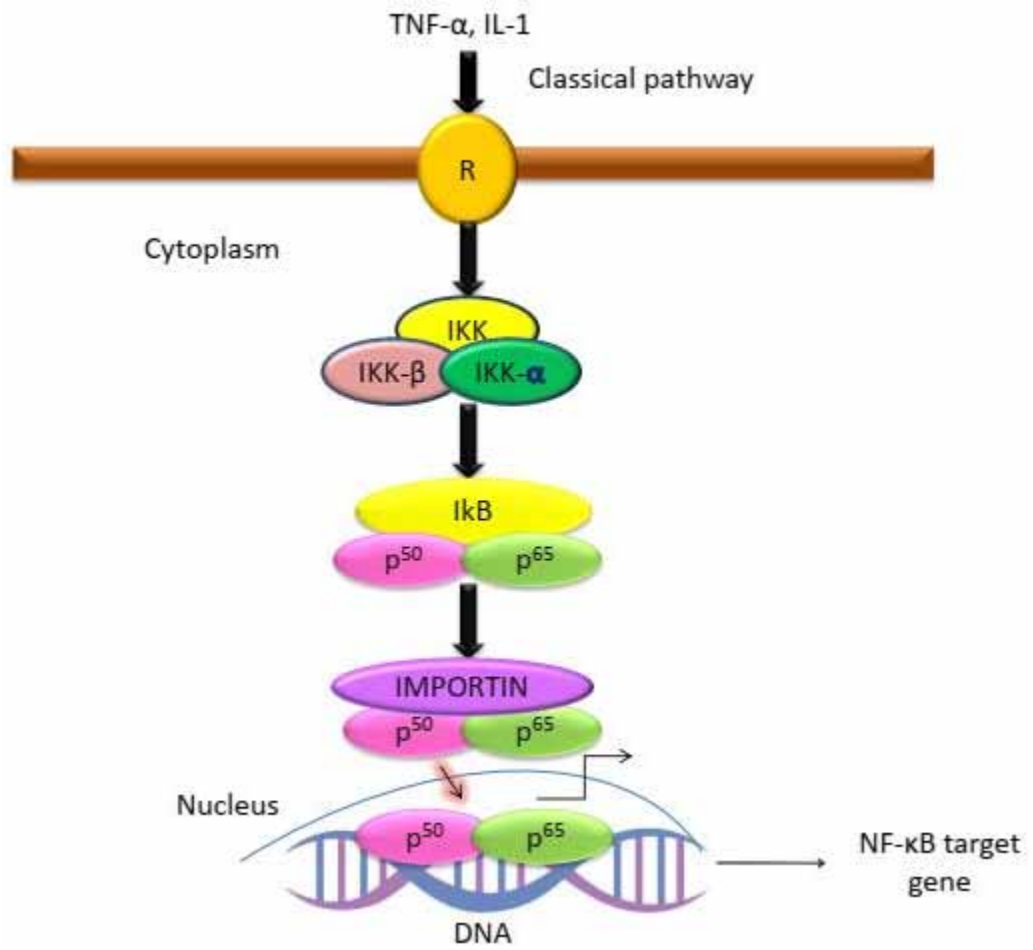
NF-κB (Nuclear Factor of Kappa Light Chain Enhancer of Activated B-cell)

NF-κB are small family of inducible transcription factors that play an important role in almost all mammalian cells. NF-κB is a cytoplasmic transcription factor, which upon induction translocates to the nucleus and remains in its active form (Perkins, 2000). Based on the previous studies it is identified that NF-κB was reported to be activated in majority of oestrogen receptor negative BCs. Suppression of NF-κB causes abnormal localization of many proteins such as Rel B, CRel, P^{50}, P^{52} and P^{65} (Figure 1). This manipulation can cause disruption of balance between cell survival and cell death (Karin and Lin, 2002).

There are two major signaling pathways associated with NF-κB - classical (Canonical) and alternative (non- Canonical) pathway. The pathways are based on the signal induced phosphorylation and degradation of certain inhibitory molecules (Pandurangan and Mustafa, 2018). Further the activity of the pathway depends on signal activated kinase, identification of inhibitory and NF-κB molecules eventually aiding the translocation of NF-κB to the nucleus (Chua *et al.,* 2007). Based on recent studies, activation of NF-κB is required for the promotion of Epithelial Mesenchymal transition (EMT). EMT is a mechanism that leads to the progression of BC. ZEB-1 and ZEB-2 transcription factor inhibits E-cadherin expression and further lead to the progression of EMT (Huber *et al.,* 2004).

The classical pathway leads to the development of cancer. NF-κB is located in the cytoplasm until a virus, bacteria, IL-1 or TNF-α encounter the cell. Classical transcription activator of NF-kB is $p^{65}$and p^{50} which are hetrodimer proteins. p^{65} is bound to inhibitory κB (IκB). Upon phosphorylation of IκB by Serine Kinase, IkB leads to degradation thereby releasing p^{65} to the nucleus through importin protein. However, p^{50} remains in the cytoplasm and prepares itself to bind to the next p^{65} to form an active transcription factor. Another protein A20 inhibits further activation of NF-κB by binding to TNF-α and IL-1. Targeting NF-κB to treat TNBC is a promising strategy (Rayet et al., 1999). Overall, NF-κB exhibits an

Figure 1. Classical pathway of NF-κB which leads to the development of cancer



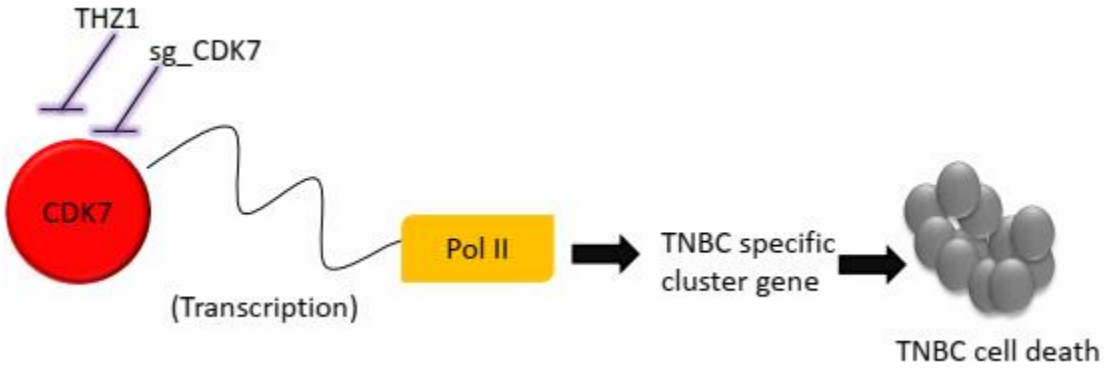
essential role in tumor development and progression in TNBC and may be used as a potential biomarker and therapeutic target.

FOXMI (Fork-Head Box Protein M1)

FOXM1 controls the expression of cell-cycle-related genes that are necessary for DNA replication and mitosis progression. In line with its role in proliferation, increased level of FOXM1 has been revealed in a variety of human tumor entities. It is mainly represented for metastasis and angiogenesis. Upregulation of FOXMI leads to the initiation of oncogenesis. FOXMI is one of the regulators for BC invasion through regulating MMP in the transcription level (Lai *et al.,* 1990). FOXM1 chemical inhibitors have been identified to restrict the spread and induce apoptosis in cancer cells *in vitro*, suggesting that FOXM1 inhibitors may be effective anticancer therapeutic agents.

FOXM1 is primarily present in the cytoplasm during the late G1 and S stages, but it is observed to be phosphorylated and translocated to the nucleus before the cells reach the G2 / M stage. The activation of the MAPK/ Raf / MEK pathway is essential for the nuclear transformation of the FOXM1 protein.

Figure 2. Potential therapy for TNBC is suggested by its strong dependence on CDK7 transcriptional kinase and the kinase-regulating gene cluster



In line with its role in fostering proliferation, increased expression of FOXM1 has previously been documented in a number of human tumors, mainly in BC. FOXM1 depletion induces a certain type of cell death called mitotic catastrophe that often occurs during mitosis due to a deviant G_2 checkpoint regulation (Gemenetzidis *et al.,* 2010).

A recent study on FOXMI denotes that, it could represent a potential prognostic breast tumor marker that could be used in multi-marker BC boards. Interestingly, it is observed that there exists a positive association between FOXM1 expression and HER2, posing FOXM1 as a new drug target for HER2 resistant breast tumors. This suggested that FOXM1 inhibitors are used in the treatment of cancers (Bektas *et al.,* 2008). More experiments are ongoing to examine the possible relationship between FOXM1 and HER2, in particular whether FOXM1 specifically stimulates the HER2 promoter.

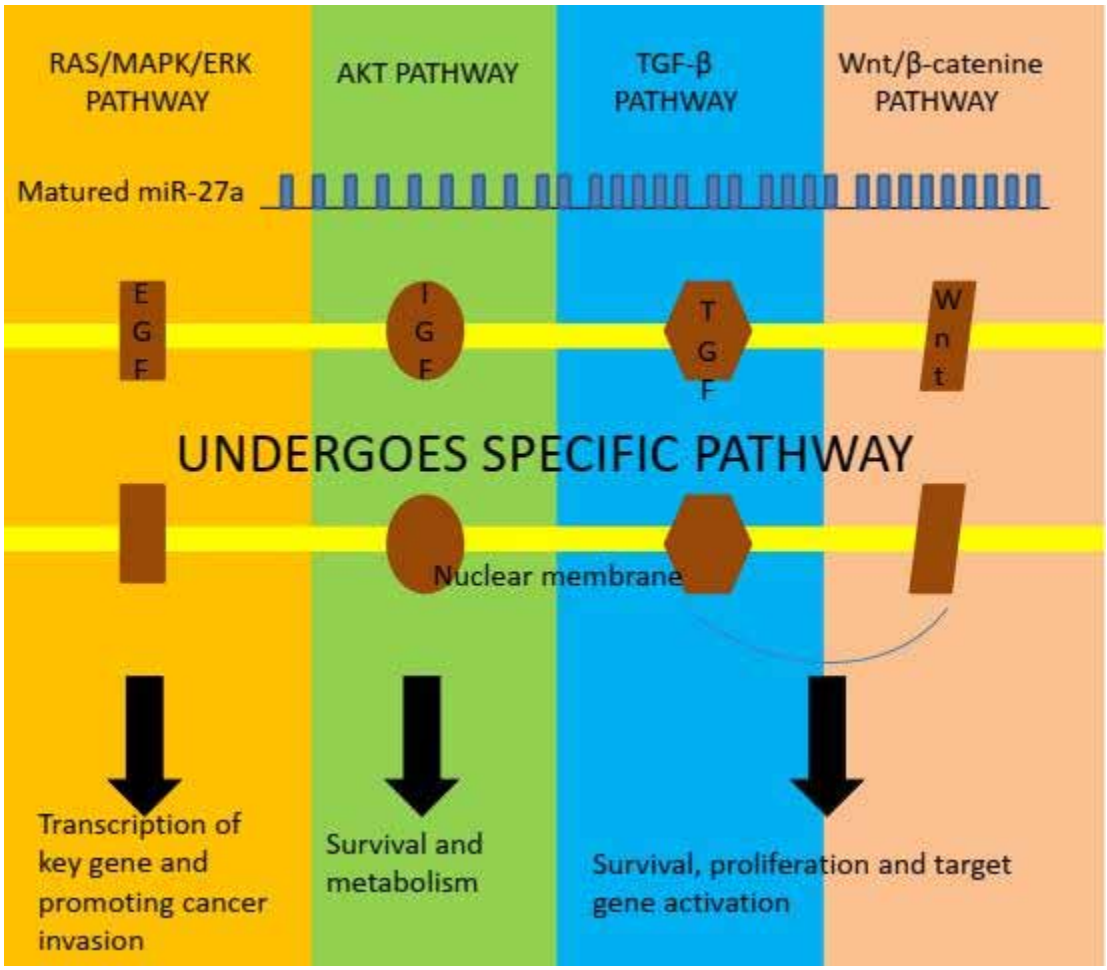
CDK7 (Cyclin Dependent Protein Kinase 7)

Cyclin-dependent kinase 7(CDK7) is an enzyme encoded by cyclin-dependent protein kinase (CDK) family of genes. Though, CDK7, is not a transcription factor category of genes, we interested to include in this chapter since it is critical in TNBC. Published reports revealed that CRISPR/Cas9-mediated gene editing states that TNBC cells shows selective dependency on CDK7 regulation. It was also proved that CDK7 activity is critical for the expression of a set of genes essential for TNBC. A covalent CDK7 inhibitor blocks tumor growth in patient derived xenografts of TNBC (Franco *et al.,* 2015).

Inhibition of CDK7 uncovered an “Achilles cluster” of genes in the TNBC transcriptional system which is likely to be responsible for making these cells selectively immune to THZ1 therapy. These genes have been identified by their overexpression in TNBC cells when compared with the ER / PR+ cells. These cells are also found to be sensitive to THZ1 and their intervention in transcriptional regulation & signaling (Figure 2) is considerably overexpressed in TNBC cells. This group includes putative oncogenes that are improperly regulated in TNBC and are key factors contributing to the tumorigenicity of TNBC (Hnisz *et al.,* 2015).

TNBC cells are unique in their reliance on this CDK transcription and undergo apoptotic cell death upon CDK7 inhibition. The “Achilles cluster” of TNBC-specific genes is particularly prone to CDK7

Figure 3. Mechanistic action of miR-27A in regulating cell signal pathway



inhibition and is often associated with super-enhancers (Franco *et al.,* 2015). This new approach suggests that CDK7 mediates transcriptional dependency on a critical gene cluster in TNBC and its inhibition could be a useful therapy for encountering this challenging cancer (Lovén *et al.,* 2013).

MicroRNA-27a (miR-27a)

MicroRNAs (miRNA / miR) are a family of small, endogenous, non-coding, single-stranded regulatory RNAs that bind to the 30-untranslated region (30-UTR) of complementary sequences. They also downregulate the translation of target mRNAs as post-transcriptional regulators. Deregulation miRNAs are involved in wide range cellular processes in TNBC. They mainly function as tumor suppressors depending on their cellular target associated with tumor initiation, promotion, malignant conversion, and metastases (Tang *et al*., 2014).

MicroRNA-27a (miR-27a), transcribed by the miR-27a gene, has been shown to affect several types of solid tumors. This emphasizes its role as a promising biomarker or drug target for therapeutic ap-

plication. Studies reveal that miR-27a has long been known as an oncomiR for BC. Overexpression of miR-27a is associated with endothelial proliferation of the stem of BC related cells. This new approach reveals that it can also control the specificity of protein transcription factors and the G2-M checkpoint in the MDAMB-231 TNBC cell line. Hence, they influence cell proliferation and apoptosis (Figure 3). IR mediated apoptosis is closely linked to cell cycle arrest, and thus, miR-27a is closely likely to be involved in radiosensitivity control of TNBC cells (Ling *et al.,* 2020). Altered microRNA (miRNA / miR) expression controls the activity and progression of tumors in TNBC cells. Recent studies have shown that miR-27a enhanced the survival of TNBC cells following irradiation. Thus, miR-27a inhibited radiation-induced apoptosis in TNBC cells by caspase regulation and Bcl-2 expression (Gottardo *et al.,* 2007).

Expression levels of PTEN and phosphorylate protein kinase B in MDA-MB-231 and MDA-MB-468 cells have been changed over miR-27a regulation. Luciferase assay showed that miR-27a regulated PTEN and BAX expression by binding to 3'-untranslated regions (Mertens-Talcott *et al.,* 2007). Lastly, miR-27a plays a crucial role in TNBC growth and progression and thus may be used as a possibl biomarker to assess radiotherapy responses and disease predictions.

MiR-27a can regulate RAS/MAPK/ERK pathway to activate key genes such as c-myc. It plays an important role in progression and promoting cancer invasion. MiR-27a can regulate AKT pathway to activate the survival signal of tumor cells. MiR-27a leads to aberrant activation of Wnt/β-catenin pathway to promote the proliferation and survival of cancer cells.

Effectiveness of Natural Agents in Treating BCs

Advanced chemotherapeutic agents used to treat various cancer forms have also reported for consecutive systemic toxicities. Hence, a new trend of practicing traditional chemotherapy is being considered. In the recent times, combination chemotherapy involving the use of a variety of chemotherapeutic agents against different biochemical/molecular targets has been able to achieve promising results by enhancing the efficacy and also reducing the ill-effects of the drugs. Therefore, an increase in research interest towards acquiring drug alternatives of natural origin possessing low toxic effects is being emphasized in recent times (Hasanpourghadi *et al.,* 2018; Anandasadagopan *et al*., 2020; Sivaprakasam *et al.,* 2020). The prime agendas in incorporating natural compounds as chemotherapeutic agents include: (i) alleviate chemotherapeutic resistance and (ii) enhance the therapeutic window of using natural products as chemotherapeutic drugs (Wang *et al.,* 2012). Various studies have supposedly shown that numerous plant extracts like matairesinol, curcumin, resveratrol and extracts of *Claviceps purpurea* and *Solanum nigrum* effectively curb drug resistance and act as chemoprotective agents when administered in combination with the existing chemical anti-cancer drugs (Lin *et al.,* 2020).

Natural Agents Against Various Transcription Factors

Curcumin

The most important ingredient and a polyphenolic compound harboring umpteen medicinal properties is curcumin. It's also known to possess anti-cancer activity against various cancers. A detailed study revealed that curcumin potentially induced apoptosis in BC cells via regulating expressions of apoptotic genes and its associated proteins (Wang *et al.,* 2016). Another study highlighted the antiproliferative effect of curcumin by the downregulation of an important transcription factor in cell proliferation - NF-κB in

both BT-483 and MDA-MB- 231 cell lines (Liu e*t al.,* 2009). The invasion and adhesion along with the metastatic traversing of the MCF-7 cells was effectively inhibited by curcumin through the activation of NF-κB. This further lead to suppressed urokinase type plasminogen activator expression (Zong et *al., 2*012). In a similar manner, many studies have proven curcumin to be a potential anti-tumor component as it effectively impacts the NF-κB signaling pathway (Bachmeier et *al., 20*08; Lin et *al., 20*04).

Genistein

Among the various compounds that can be extracted from soy products, Genistein is the most potent isoflavone. It is known to possess anti-tumor properties against many cancer forms (Banerjee e*t al.,* 2008; Messing e*t al.,* 2012). Its structural resemblance to estradiol (E2) enables its binding and activation of both ERα and ERβ thereby exhibiting estrogenic effects. This results in reduced risk of BC occurrence in the soy consuming population. Experiments on MCF10A (human breast epithelial) cells revealed that genistein effectively blocked the ERK associated phosphorylation of p65. This further leads to hindered NF-κB transcriptional activity along with the downregulated expression of TPA-associated COX-2 gene. Therefore, Genistein is considered to be a potential chemotherapeutic agent against BCs. Furthermore, it is also proven that genistein is a potential ER modulator like raloxifene and tamoxifen, which are among the commonly used drugs to prevent and treat BCs (Mitra and Dash, 2018).

Shikonin

Studies on Shikonin, predominantly present in the root extracts of Li*thospermum erythrorhizon, h*ave shown that it exhibits many biological effects inclusive of anticancer, wound healing, anti-inflammatory, antiviral like properties. Shikonin is known to induce apoptosis via NF-κB pathway suppression, caspase-3 activation and modifications in the Bax & Bcl-2 apoptosis-related genes (Dash et *al., 20*17). Another study has demonstrated the role of Shikonin in the suppression of NF-κB pathway via inhibiting IκB- α phosphorylation and p65 downregulation (Duru et al*., 2014).*

Rosmarinic Acid

Rosmarinic acid (RA) is a key polyphenolic compound isolated from the spice herb rosemary (Rosm*arinus officinalis). I*t possess eminent anti-cancerous properties against breast and many other cancers (Yesil-Celiktas et a*l., 201*0). RA has demonstrated apoptotic effects on BC cells single-handedly (Li et a*l., 201*8) and has also shown to augment the apoptotic effect of the chemotherapeutic agent Adriamycin (Huang et a*l., 201*8). Another such study highlights the role of RA in the NF-κB pathway where it effectively diminishes interleukin-8 (IL-8) levels eventually inhibiting bone metastasis in breast cancers (Wang et al*., 2012*). Experiments on MDA-MB-468 cells have shown that RA triggers BNIP3, a proapoptotic gene through intrinsic and extrinsic caspase-independent apoptosis pathways. RA facilitates cell cycle arrest in the S-phase as it potentially suppresses BIRC5 and triggers BNIP3, TNF and GADD45A. Similarly, in the MDA-MB-231 cell line, RA was seen to upregulate TNFRSF25, BNIP3 & HRK and downregulate TNFRS*F11B (Mes*seha et al*., 2020*).

Tocotrienols

Tocopherols and Tocotrienols are important fractions with structural similarities belonging to the vitamin E family, yet various studies prove that only tocotrienols possess anti-cancer properties. The anti-tumor mechanism of action of a Tocotrienol-Enriched Fraction (TEF) and a Tocotrienol-Rich Fraction (TRF) extracted from palm oil were experimented on MCF-7 cells and MDA-MB-231 cells. Also, the effects of analogues of vitamin E (α−, δ− & γ−tocotrienols and α-tocopherol) were tested on the above said cell lines. They revealed the fact that they displayed anti-proliferative effects via apoptosis induction. They effectively cleaved the DNA repair protein poly (ADP-ribose) polymerase which in-turn inhibited the Nuclear Factor kappa-B (NF-κB) signalling pathway leading to apoptosis (Loganathan et *al., 20*13).

Lambertianic acid

A natural compound of significance extracted from the P*inus koraiensis* is Lambertianic Acid (LA) which possesses anti-cancer effects against many cancer forms. A recent study conducted on MDA-MB-231 cells signifies that LA exerts cytotoxic effects on MDA-MB-231 cells. It enhances the sub-G1 population, induces cell cycle arrest at the G2/M phase and down-regulates FOXM1, XIAP, CyclinB1, Bcl-2, p-AKT & pro Caspase3. It was also found to up-regulate p-ACC (acetyl-CoA carboxylase pathway) and p-AMPK (AMP-activated protein kinase) pathways. It was also found that LA effectively interrupted the AKT - FOXM1 binding thereby highlighting the fact that the MDA-MB- 231 cells experienced LA-induced apoptosis (Lee e*t al.,* 2018).

Moracin D

Moracin D is a 2-arylbenzofuran flavonoid that can be extracted from *Morus alba.* They are rich sources of isoprenylated flavonoids, Diels-Alder adduct compounds, stilbenes, 2-arylbenzopyrans and coumarins like compounds. They exhibit antioxidant and anti-inflammatory properties and is hence used to treat heart diseases, cough and diabetes like conditions. It has also shown to display cytotoxicity in MDA-MB231 cells via increasing the sub-G1 population, cleaving of PARP and down-regulating cyclin D1, pro-caspase 3, XIAP and Bcl-2 expressions. Recent finding also proves that Moracin D significantly inhibited FOXM1, Wnt3a and β-catenin expressions thereby effectively leading to apoptotic cell death (Hwang *et al.,* 2018).

Maslinic acid

Maslinic acid (MA) is a natural triterpene which harbors anti-cancer properties. Various researches prove that it effectively regulates metabolism, cell growth and apoptosis in various cancer forms like BC (Alam *et al.,* 2017), colorectal cancer (Yoo *et al.,* 2015), hepatocellular cancer (Ku *et al.,* 2015) and gastric cancer (Lee *et al.,* 2015). A study conducted on Maslinic acid has shown that it enhances the anti-cancer ability of conventional chemotherapeutic compounds or inverses tumor cell's chemoresistance towards conventional chemotherapeutic agents (Yu *et al.,* 2015). Another such study on human docetaxel-resistant MDA-MB-231 cells emphasized that MA effectively reversed the resistance to DOC when used as a combination therapy by increasing the accumulation of cellular DOC (Wang *et al.,* 2020).

Casticin

Casticin, an extract from the medicinal plant *Vitex trifolia (L.),* (family: Verbenaceae) of Chinese origin has shown to harbor anti-cancer property. It targets the FOXO3a/FOXOM1/survivin signalling pathway in the cancer cells. A study conducted on MDA-MB-231 cells demonstrated that casticin hindered the phosphorylation of FOXO3a in the cytoplasm, along with the inhibition of two FOXO3a downstream proteins of immense importance, namely survivin and FOXM1 (Liu *et al.,* 2014).

Vernodalin

The seed extracts of a member of the Asteraceae family - *Centratherum anthelminticum (L.)* kuntze, commonly known as the black or bitter cumin, is an abundant source of vernodalin. Studies on BC cell lines have shown the anti-tumor activity of vernodalin as it targets FOXO3a which in-turn affects the expression of the transcription factor FOXM1 (Arya *et al.,* 2012; Looi *et al.,* 2013). Increased FOXO3a accumulation in the nucleus along with the up-regulation of Bim followed by Bax activation, facilitated induction of apoptosis upon vernodalin administration in both MDA-MB-231 and MCF-7 cell lines (Sadagopan *et al.,* 2015).

Wogonin

Wogonin is a flavone of immense importance that can be extracted from the Chinese medicinal plant *Scutellaria baicalensis Georgi,* commonly known by the name Huang-Qin. When tested, wogonin seemed to express cytotoxic effects against many tumor cell-lines (*in-vitro* analysis) and also prevented tumor progression in mouse models (*in-vivo* analysis) (Li-Weber, 2009). Similar studies were performed on human subjects with breast carcinoma in advanced stages (clinical trials) where wogonin exhibited no or little cytotoxicity on normal cells (Perez *et al.,* 2010; Rugo *et al.,* 2007; Wang *et al.,* 2006). CDK7 is an important component of the transcription factor TFIIH facilitating transcription initiation. It enables Ser5 residue phosphorylation in the carboxy-terminal domain's heptad repeats in the RNA polymerase II (RNAPII) (Wang and Fischer, 2008; Shapiro, 2006]. Upon wogonin treatment, the level of RNA synthesis was drastically reduced. Subsequent accelerated downregulation of Mcl-1 which is a short-lived anti-apoptotic protein myeloid cell leukemia 1, was also observed which eventually leads to apoptosis in tumor cells (Polier *et al.,* 2011).

Triptolide

An important bioactive component from the extract of *Tripterygium wilfordii Hook F* is triptolide which possess anti-cancer, anti-inflammatory, antifertility, immunosuppressive and anti-cystogenesis like properties (Zhou *et al.,* 2012). Studies report triptolide to be a novel sect of transcriptional factor inhibitors as they distinctly down-regulated RNA polymerase II (RNAPII)–dependent transcription (Titov *et al.,* 2011). Cancer cell lines upon treatment with triptolide effectively hindered the hyperphosphorylation of Rpb1 in the Ser-5 residue, thereby lowering the expression of Cdk7 and its associated siRNA. This eventually facilitates the degradation of both the total RNAPII and the RNAPII bound to the promoters of the transcribed genes like the polr2a, hif-1a, vegf and myc genes (Manzo *et al.,* 2012).

Betulinic acid

3β-hydroxy-lup-20 commonly known as betulinic acid is a lupane-type pentacyclic triterpenoid saponin extracted from the barks of *Betula pendula.* It is found to express enormous beneficial properties such as immunomodulatory, anti-angiogenic, anti-inflammatory and anti-cancerous potential against varied cancers, breast carcinoma included (Tiwari *et al.,* 2014; Zhang *et al.,* 2016). Studies conducted on MDA-MB-231 reveal the hindered mRNA expressions leading to low levels of Sp1, Sp3 and Sp4 proteins, thereby triggering apoptosis eventually (Li *et al*., 2014; Mertens-Talcott *et al.,* 2013). Another study in similarity, highlighted the inhibitory effects of betulinic acid on MDA-MB-453 and BT474. Here, the expression of Yin Yang 1 (YY1), a gene which is Sp-regulated was predominantly down-regulated by the activation of CB1 and CB2 (Cannabinoid type) receptors. Similarly, a prominent upstream ErbB2 regulator was also found to be down-regulated (Liu *et al.,* 2012). A recent study on T47D and MCF-7 cell lines reported that betulinic acid played a crucial role in triggering apoptotic cell death in a p53-independent manner (Shi *et al.,* 2010).

Pomogranate Polyphenols

Polyphenolic compounds extracted from the peels and juice of the pomegranate fruit have proven to inhibit aromatase activity involved in the progression of BCs (Kim *et al.,* 2002; Sreeja *et al.,* 2011). It has been reported from various studies that the transcription factor miRNA 27a kindled an increased Specificity protein (Sp) expression in the BC cells by down-regulating the expression of a Sp-repressor - ZBTB10. This causes cell survival and progression. However, upon pomegranate extract treatment, the MDA-MB-231 and BT474 cells accounted for decreased Sp (Sp1, Sp3, and Sp4) levels and increased ZBTB10 expressions because of the down-regulation of miRNA 27a (Banerjee *et al.,* 2012).

CONCLUSION

BC is considered to be one among the most prevalent ten cancers occurring globally and is related to varied range of genetic mutations. An increased proportion of various oncogenes and other genes related with tumor suppression affect the associated transcription factors which supposedly play an important role in the control of cell cycle, invasion and cell death. This proves the fact that they act as potential targets for cancer therapies. In comparison to the chemically synthesized drugs, various biologically active compounds of natural origin seem to possess desirable traits. Structures with lead specificity and cancer cell sensitizing ability when combination therapy is used, without causing much harm to the surrounding normal cells are few of the notable traits. Hence, curcumin, genistein, vernodalin, wogonin, etc are few among the biologically active natural compounds used in traditional medicines for decades which are being extensively studied in recent times by the pharmaceutical realm in order to obtain sustainable novel drugs against various diseased conditions. A better understanding of the structural properties of such compounds of natural origin and elucidation of its mode of action in relation to its molecular (transcriptional factors) and cellular (signaling pathways) aspects may pave way for novel drugs with better capabilities against various cancers.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Chapter 2
Natural Products and Their Bioactive Compounds as Breast Cancer Therapeutics

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ABSTRACT

Breast cancer is one of the most common types of cancer in the Western world. It is cancer that is curable and has great life expectancy afterwards, but the treatment often combines surgery with chemotherapy and/or hormone therapy. This creates a need for more effective and less toxic therapeutic and preventive strategies for breast cancers as well as strategies to overcome increasing resistance to hormonal and targeted therapy. This chapter focuses on chemopreventative and anti-cancer activities of different bioactive compounds obtained from dietary sources, herbal approach, and use of natural compounds such as diindolylmethane, biochanin A, curcumin, Epigallocatechin Gallate, genistein, lycopene, shikonin, sulforaphane, and resveratol. Understanding the pathophysiology of action of these compounds and their potential preventive and therapeutic effects on cancer may provide a rationale for further studies.

INTRODUCTION

Cancer ranks as a leading cause of death in many countries around the world. According to estimates from the World Health Organization (WHO) in 2019, (WHO, 2020) cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries. In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. Improvements in survival following diagnosis of breast cancer began in the 1980s in countries with early detection programmes combined with different modes of treatment to eradicate invasive disease. (De Santis et al., 2015) Breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women. Data reports from various latest national cancer

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registries were compared for incidence, mortality rates. The age adjusted incidence rate of carcinoma of the breast was found as high as 41 per 100,000 women for Delhi, followed by Chennai (37.9), Bangalore (34.4) and Thiruvananthapuram District (33.7) (Nandakumaret al., 2005; Swaminathan et al., 2009).

Breast cancer treatment can be highly effective, achieving survival probabilities of 90% or higher, particularly when the disease is identified early. Treatment generally consists of surgery and radiation therapy for control of the disease in the breast, lymph nodes and surrounding areas (locoregional control) and systemic therapy to treat and/or reduce the risk of metastasis. The systemic treatment of breast cancer in general has come a long way in delivering more targeted hormone/chemo therapy. The advancement is due to better understanding and research into the pathophysiology of breast cancer and we can now influence the pathway with non-surgical treatment. Surgery, chemotherapy, radiotherapy, and hormone therapy are the most frequently used methods of treatment for breast cancer. However traditional treatment with chemotherapeutic drugs has faced the development of drug resistance, the occurrence of side effects, and reoccurrence of the disease which indicates that these drugs have limited efficacy. Scientists are turning to agents with more efficacy, such as natural compounds for treatment and prevention. Selected natural compounds, promote apoptosis and inhibit metastasis, preventing cancer growth. As a result, these compounds have the potential to suppress breast cancer progression, thus increasing patient survival rates and decreasing the number of related deaths. This chapter provides overview of natural compounds that have displayed, anti-cancer effects on breast cancer cells in various studies. These natural compounds inhibit the development of breast cancer, suppress the growth of cancer cells, and promote cell death. (Li et al., 2017)

TRADITIONAL TREATMENT OPTIONS OF BREAST CANCER

The treatment of breast cancer has evolved rapidly over the years. From simple surgery, it has now moved to a multidisciplinary approach involving surgeons, clinical and medical oncologists and radiologists, breast care nurses, etc.

Due to the underlying and still advancing knowledge of breast cancer, we have a wide range of treatment consisting of (Moo et al., 2018):

- surgery
- radiotherapy
- chemotherapy
- hormone therapy
- immunotherapy
- targeted therapy.

These methods of treatment are often used in combination and targeted towards the specific pathology of a patient (usually as a result of core biopsy), taking into consideration other factors (for example, staging, comorbidities and patient's wishes). There are several predictive tools to aid the clinical decision towards chemotherapy.

These modalities of treatment are not risk free and are often associated with multiple side effects. The reduction of side effects might be a key to successful and less harmful treatment of breast cancer.

Another hurdle is created by increasing the number of chemotherapy-resistant breast tumours, where further research is needed to try and affect sensitivity of cancer to drug therapy.

In recent years, much research has been focused on chemopreventive and anticancer activities of different bioactive compounds obtained from dietary sources, herbal approaches and use of natural compounds (such as diindolylmethane, biochanin A, curcumin, Epigallocatechin Gallate, genistein, lycopene, shikonin, sulforaphane and resveratol). (Subramaniam et al., 2019) Some of these compounds show great potential and are likely to play an important role in enhancing survival rates in the future.

NATURAL PRODUCTS AND THEIR BIOACTIVE COMPOUNDS: TREATMENT OPTIONS OF BREAST CANCER

Breast cancer has an increasing rate of incidence worldwide. Although the survival rate is very good, there is a large number of exogenous and endogenous factors that can influence the incidence of breast cancer and/or its response to treatment. The treatment of breast cancer traditionally consists of at least one, but usually a mixture, of the following modalities that bring about various side effects – surgery, chemotherapy, radiotherapy, and hormone therapy immunotherapy. A lot of research is now focused on the most targeted and less harmful way of treatment, as well as chemoprotective agents (Sharma et al., 2010). Much of the anticancer medication has been derived and developed from plant-based ingredients and this field has shown a massive potential. Natural products and their derivates have been explored in many different ways, focusing on the treatment of breast cancer as well as its prevention. Some recent studies have suggested the benefit of dietary natural compounds in the prevention of breast cancer (Grosso et al., 2017). There is also an improved response to conventional treatment when using some of the natural products.

Mechanisms of action of studied phytochemicals suggest either direct targeting of specific molecules or indirect stabilisation of conjugates and, therefore, affecting metabolic pathways. In 2013, it has been reported that some herbal compounds could be used alongside chemotherapy to prevent side effects. (Liao et al., 2013) It has been proved that phytochemicals can act as alteration agents in the cell cycle, initiator and apoptosis and re-activator of tumour-supressing genes. This effect is usually achieved by targeting specific metabolic pathways, transcription factors, kinases or growth factor receptors.

A comparison of synthetic drugs and natural compounds favoured natural compounds in chemoprevention by expressing less side effects and toxicity. (Aung et al., 2017)

A lot of research has been carried out in the alteration of aromatase expression and cyclooxygenases (especially COX-2) pathways (Khan et al., 2011) as there is an association between unaltered pathway and worse prognosis or metastatic disease in mice. A number of phytochemicals such as curcumin, ginsetin, lycopene, and apigenin have been directly reported to inhibit biosynthesis of metabolic products such as prostaglandins and leukotrienes and, therefore, have been considered as the potent therapeutic agents in breast cancer chemoprevention. Further research showed some positive effects of phytochemicals in the modulation of extrinsic and intrinsic pathways of apoptosis. (Rahman et al., 2021) Targeting proteins that have a direct effect in apoptotic pathways is considered very promising in future anticancer treatment. Another method is targeting the inhibition of growth factors stimulating cancer cells.

3,3′-DIINDOLYLMETHANE (DIM)

3,3′-Diindolylmethane (DIM) is a natural compound converted in a highly acidic environment from indole-3-cabinol. Indole-3-canbinol occurs naturally in the cabbage family of vegetable such as broccoli, cauliflower or cabbage. The conversion is initiated by high HCl concentration and low pH in the stomach following digestion.

DIM can be considered an anti-initiating agent through its ability to stimulate cellular detoxification pathways. DIM is reported to modulate aryl hydrocarbon receptor (AhR), as evidenced in multiple breast cancer cell lines. (Chen et al., 1998) AhR is a ubiquitous cytoplasmic receptor that, when activated and transported to the nucleus, promotes transcription of genes that stimulate the expression of detoxification enzymes, including the phase I cytochrome P450 (CYP) family. Cellular responses to AhR signaling can either promote or diminish inflammation. DIM has an affinity to bind to the AhR. (Jellinck et al., 1993) Modulation of AhR by DIM treatment has also been shown to stimulate the Nrf2-mediated phase II response, which enhances excretion of genotoxins and induces a significant antioxidant response. (Banerjee et al., 2011) Through the activation of AhR and Nrf2 signaling pathways, DIM effectively increases detoxification and reduces inflammatory signaling, blocking what could otherwise be cancer-initiating events. Furthermore, modulation of AhR by DIM inhibited the growth of mammary gland cell cancer, an action suggested as a mechanism of crosstalk between estrogen receptor α and AhR. (Schlezinger et al., 2006)

The influence of DIM on the AhR results in a change in gene activity that reduces the induction and activity of the enzyme cyclooxygenase-2. (Degner et al., 2009) Evidence from mammary cell lines has demonstrated the role of DIM in reducing oxidative stress by stimulating the phosphorylation of BRCA1 (Fan et al., 2009). Further, DIM has a demonstrated role in reducing cyclooxygenase-2–induced inflammation in mammary cell lines. (Degner et al., 2009) In advanced stages of tumor development, DIM has been shown in tumor cell line models to inhibit the expression of genes involved in angiogenesis and energy metabolism, including those involved in the induction of surviving (Rahman et al., 2006) and hypoxia-inducible factor-1. (Riby et al., 2008)

The effects of DIM on transcription and proliferation are mediated by estrogen receptor α and are evident at a concentration of 1μM.(Wang et al., 2006) However, in the notable absence of estradiol, concentrations of DIM at 10μM have been shown to activate estrogen receptor α signaling pathways in human breast cancer cell lines in vitro, increasing cellular proliferation in an estradiol-independent manner, yet an opposite effect (growth arrest) can be demonstrated when higher concentrations of DIM (50μM) are provided. In estrogen-dependent and estrogen-independent breast cancer cell lines (MCF-7 and MDA-MB-231, respectively), DIM has been observed to arrest proliferation, possibly through arrest of de novo cell lipogenesis or induction of Wnt signaling pathways. (Saati, Archer, 2011) DIM may also act as an aromatase inhibitor. It was efficient at decreasing aromatase expression in MCF-7 cells and also upregulated *CYP19* expression, which encodes aromatase and synthesizes estrogens in MDA-MB-231 cells. (Licznerska et al., 2013)

In combination with Taxotere, a concentration of 40μM DIM resulted in a 78% inhibition of growth and a decreased invasive capacity of the aggressive breast cancer cell line MDA-MB-231; these findings were associated with decreased activation of FoxM1. MDA-MB-231 cells express higher levels of FoxM1 than MCF-7 breast cancer cells. Cells treated with DIM showed reduced FoxM1 mRNA levels. Downregulation of FoxM1 expression induced the growth-inhibitory effect of DIM, suggesting a mechanistic role of FoxM1 and a regulatory role of DIM. (Ahmad et al., 2011)

More recently, DIM has been demonstrated to protect against ionizing radiation through activation of the protein kinase ataxia telangiectasia mutated (ATM), which regulates responses to DNA damage and oxidative stress as well as cell survival signaling through nuclear factor-κB (NF-κB). (Fan et al., 2013)

BIOCHANIN A

Biochanin A is red clover isoflavone which has shown great potential in cancer treatment. It has been proven in lab conditions that biochanin A is able to block aromatase enzymes and therefore affect cell growth. In ER negative breast cancer patients, this compound has also shown an ability to reduce mRNA expression. (Moon et al., 2008)

Biochanin A metabolises into genistein which has the potential to suppress promoter I.3/II activation and functions as an aromatase inhibitor. The reason for the usage of biochanin A instead of its metabolite genistein was better tolerance reported by patients. Biochanin A has a positive effect on expression of tumour suppressor genes in ER positive breast cancer. This effect has better induction of expression when compared to genistein itself.

Further studies showed biochanin A affecting signalling pathways and invasive enzyme expression, as well as decreasing the growth of oestrogen-dependent tumours. Although these results look very promising, further research has to be done into other pathways of breast cancer progression. The effect of biochanin A is different in breast cancer types, therefore further studies are required to understand bioavailability and look for optimal therapeutic regimes taking into account the different types of breast cancer. At present, the most experimental studies are focused on ER positive breast cancer and further research is required into ER negative and triple negative breast cancer (Chen et al., 2015).

GENISTEIN AND OTHER SOY ISOFLAVONES

Genistein is isoflavone from soy and also metabolite of biochanin A. It has proved to be a very potent dietary component in decreasing the incidence of various cancer types. It has been known and trialled as a chemopreventive agent for various cancers (e.g. bladder cancer). (Messina, Wood, 2008)

The compound overcomes cancer drug resistance and suppresses the recurrence of cancers. (Fan et al., 2013) It also reduces tumorigenesis of cancers that require estrogen. Genistein induces cell differentiation and inactivation of the epidermal growth factor signaling pathway (Zhang et al., 2015). In addition, it has anti-oxidation, anti-proliferation, anti-cancer activities; it also promotes apoptosis and suppresses angiogenesis and metastasis. Genistein is thought to modulate gene transcription by regulating epigenetic activities (Latocha et al., 2014). Furthermore, it suppresses topoisomerase I and II and DNA polymerase II, and it downregulates genes encoding cyclins, such as B1, D1, CDK-1, and Wee1. Genistein inhibits expression of Bcl-2, IAP, XIAP, and survivin, which are inhibitors of apoptosis. Moreover, for cancer cells, it increases expression of p53, p21, p27, and p16 and suppresses tyrosine kinases, thus inhibiting cell survival and cancer progression. (Xie et al., 2014)

Genistein downregulates global DNA methylation levels, DNA methyltransferase (DNMT) activity, and DNMT1 expression levels (Xie et al., 2014). It interacts with the catalytic domain of DNMT1 and thereby suppresses the binding of hemi-methylated DNA to the catalytic domain of DNMT1. In addition, genistein reduces DNA methylation in the promoter area of various tumor suppressor genes by upregu-

lation of their mRNA expressions (Xie et al., 2014). It also reduces breast cancer stem cells (BCSCs) and breast cancer stem-like cells by downregulating the Hedgehog-Gli1 signaling pathway. Blocking of this pathway reduces CSC survival by lowering of the proteins, SMO and/or Gli1. Downregulation of the Hedgehog-Gli1 signaling pathway and ALDH1 is associated with a decrease of the stemness of BCSCs. Thus, by decreasing the expression of these BCSCs, which are involved in drug resistance, cancer relapse, and metastasis, genistein prevents a primary cause of cancer, making it an effective preventive agent for breast cancer (Fan et al., 2013).

Genistein suppresses breast cancer cell growth and stimulates apoptosis by promoting the inactivation of IGF-1R and p-Akt. Moreover, it decreases the Bcl-2/Bax ratio, suggesting that it can prevent BrCa progression (Liu et al., 2016). It promotes differentiation of BCSCs by interacting with ER+ cancer cells. In addition, for T47D cells, genistein decreases the expression of MMP-2, MMP-3, MMP-13, MMP-15, TIMP-1, TIMP-2, and TIMP-3. Thus, it prevents BrCa angiogenesis and metastasis. In clinical practice, this compound has the potential to increase survival rates of patients with breast cancer (Latocha et al., 2014).

Some studies suggested that genistein causes an increase of regulation of BRCA1 and BRCA2 mRNA expressions in adult ovariectomised rats. On the other hand, the use of genistein in non-active BRCA1 mice showed a reduction of tumour size by 50%. This indicates a great potential of genistein in the absence of active BRCA1. (Shim et al., 2007)

The biggest pitfall reported by multiple studies is the low oral bioavailability of genistein. More research will be necessary before the recommendation of genistein in breast cancer therapy.

CURCUMIN

Curcumin is polyphenolic compound and active ingredient of turmeric. It has historically, and in research, a vast spectrum of medical use including the prevention/treatment of breast cancer.

For breast cancer cells, curcumin has a wide range of effects. Either alone or in combination with other natural compounds or chemotherapeutics, hinders tumorigenesis and cancer cell growth. For instance, curcumin reduces proliferation of human BrCa cells by preventing the activation of nuclear factor kappaB, which is associated with cancer cell survival, cell growth, and metastasis. Furthermore, in BT-474 and SK-BR-3 cells, CUR downregulates MAPK, and NF-κB. (Bimonte et al., 2015)

Curcumin reduces paclitaxel-induced NF-κB by inhibiting the activation of IκBα kinase and through IκBα phosphorylation and degradation. It also downregulates the expression of anti-apoptotic proteins, such as BCL-xL and BCL-2; proliferative proteins, such as cyclin-D1 and c-Myc; and metastatic proteins, such as vascular endothelial growth factor and intercellular adhesion molecule-1. (Aggarwal et al., 2005)

Curcumin reduces expression of the inflammatory cytokines, CXCL1 and −2, which results in a decrease in breast cancer metastasis. Moreover, in breast cancer metastasis is regulated by the expression of a variety of miRNAs, including miR181b, which diminishes the expression of CXCL1 and −2 by binding to their 3'-UTRs.This is relevant to its anticancer activity against breast cancer cells (Kronski et al., 2014).

Curcumin enhances the expression of Nrf2, a regulator of antioxidant defense systems in breast cancer cells and decreases expression of the Flap endonuclease 1 (Fen1) protein, a DNA-repair nuclease. Additionally, it causes Nrf2 translocation from the cytoplasm to the nucleus and suppresses Fen1-induced

activity through reduced recruitment of Nrf2 to the Fen1 promoter. Curcumin reduces the proliferation of BrCa cells, providing a new strategy for the inhibition of tumor growth. (Chen et al., 2014)

As it stands, curcumin has great potential in breast cancer treatment. However, similar to the previous compounds, the main issue remains with bioavailability. Further research is required into an increase of bioavailability or to look for more suitable analogues.

EPIGALLOCATECHIN GALLATE

Epigallocatechin gallate (EGCG) is a phenolic catechin derived from green tea and which has multiple known health benefits.

Anti-tumorigenic activities attributed to exposure to EGCG include inhibition of cell proliferation and tumor growth, induction of apoptosis and cell cycle arrest, (Lu et al., 2002) inhibition of invasion and metastasis, (Lee et al., 2007) and suppression of angiogenesis. (Cao, Cao, 1999) Treatment with EGCG reduced the growth of MCF-7 implanted breast tumors in athymic nude mice by 40% (Liao et al., 2015), and it has been reported that catechin inhibited the proliferation of human breast cancer cells in vitro. (Belguise et al., 2007) However, the underlying mechanisms are still not entirely clear.

Previous study has reported that EGCG upregulates the expression of microRNA (i.e. miR-210) by binding HIF-1α, resulting in reduced cell proliferation and anchorage-independent growth. (Wang et al., 2011) EGCG induced nuclear accumulation and transcriptional activity of nuclear factor erythroid 2-related factor 2 (NRF2), as well as binding of NRF2 to the antioxidant response element sequence located at the target gene promoters in human MCF10A breast epithelial cells. (Thomson et al., 2016)

During several trials, EGCG showed to have no effect on aromatase activity. However, from further studies, there are some suggestions of increased sensitivity to ionizing radiation protection against toxic adverse effects of chemotherapy and radiotherapy. In combination with standard treatment, EGCG has a significant effect on the bioavailability of tamoxifen, 5-fluorouracil and doxorubicin. While trialling with other anticancer medication, there were reports of interactions with EGCG. Further clinical research is required into this problematic. (Luo et al., 2010)

LYCOPENE

Lycopene is red carotene pigment that naturally occurs in tomatoes, carrots, watermelons, papayas and cherries. It belongs to the tetra terpenoids group and is a very potent antioxidant. As such, it has an effect on DNA repair mechanism, control of cell cycle, and apoptosis in breast cancer cells.

It was observed that lycopene upregulates the expression of GSTP1 and has the ability to demethylate GSTP1 promoter in MDA-MB-468 cell line; however, the scenario is not similar in MCF-7 breast cancer cells. The expressions of other genes such as RARβ2 and HIN1 remained unaltered by lycopene treatment in MCF-7 and MDA-MB-468 breast cancer cells (King-Batoon et al., 2008). In addition, lycopene can induce cell apoptosis and exert antitumor effects by regulating cell growth factor signaling pathways and thereby activate cell cycle arrest. Lycopene was also found to suppress cyclin D1 with the upregulation of p21 and also sustained the activation of the ERK1/2. The antiproliferative mechanism of lycopene in MCF-7 cell linesis regulation of the expression of p53 and Bax and thereby reduced the cell proliferation and increased apoptosis. (Peng et al., 2017)

The mechanisms of lycopene in case of ER subtypes still remain controversial, where one group reported the negative correlation of lycopene and other carotenoids with ER negative subtypes, (Zhang et al., 2012) while other groups demonstrated that consumption of carotenoids like lycopene could diminish the risk of the ER negative subtypes. (Eliassen et al., 2012) Therefore, more studies are still necessary to elucidate chemopreventive mechanism of lycopene in other pathways as well as in different breast cancer subtypes.

Acting as an antioxidant, there are studies to support the daily use of naturally occurring lycopene in prostate cancer. However, the health benefits of lycopene and its use in chemoprevention are yet to be studied.

SHIKONIN

Shikonin is a compound isolated from the root of the perennial plant *Lithospermum erythrorhizon* that is native to Japan, Korea and China. It has been used in traditional medicine for its anticancer, anti-inflammatory, wound healing, antiviral and other medical effects.

In breast cancer pathway, shikonin was found to inhibit estrogen stimulated cell growth and initiates ER ubiquitination which in turn activates ER degradation in ER-positive breast cells. (Yao, Zhou, 2010) Shikonin inhibits pS2 and c-myc and estrogen responsive gene promoters in breast cancer cell and also make protection against estrogen induced DNA damage by triggering the Nrf2 pathway (Yao et al., 2010).

In ER-positive breast cancer cell, shikonin induces apoptosis with the characteristics of necroptosis (Han et al., 2007) and also decreases the expressions of steroid sulfatase genes.

Furthermore, shikonin also increases the chemosensitivity of taxol in ER-negative human breast cells, inducing the cell cycle arrest at the G2/M phase, and also inhibits the activation of ERK, Akt, and p70S6 kinases, which are the major player of cancer drug resistance. (Li et al., 2014)

Studies showed that shikonin decreases tamoxifen resistance by inducing uc.57 in MCF-7R breast cancer cells that inhibits PI3K/Akt and MAPK signaling pathways through downregulating BCL11A. (Zhang et al., 2017)

As with the other natural compounds, the bioavailability of shikonin is an issue. Furthermore, there is an extensive metabolising process of shikonin, leaving only a limited amount of active substance. Further research is required as it is believed shikonin can have great potential in the treatment of breast cancer.

SULFORAPHANE

Sulforaphane (SFN) is an isothiocyanate commonly found in broccoli, water cress, cabbage, and kale. It has been proven to be able to inhibit proliferation, angiogenesis and metastasis as well as induce cell cycle arrest and apoptosis in breast cancer. (Kuran et al., 2020)

Studies showed that SFN exerts chemopreventive action by inducing cell cycle arrest at G2/M phase through increasing the expression cyclin B1 and activates the poly(ADP-ribose) polymerase 1 and caspase family proteins followed by apoptosis in human breast cancer cell lines. (Jackson, Singletary, 2004) SFN inhibits tubulin polymerization in breast cancer cells.(Jackson et al., 2004)

It has been demonstrated that SFN enhanced the sensitivity of tamoxifen by epigenetic reactivation of *ERα* in ERα-negative breast cancer. (Li, Meeran, 2017) Furthermore SFN inhibits the expression of

nuclear factor kappa B and COX-2 through blocking of signaling pathways mediated by ERK1/2-IKK-α and NAK-IKK- β. (Kim et al., 2014)

SFN has proven to have a chemopreventive effect on breast tissue and this is dose dependent. In low doses, SFN has great bioavailability, but this is significantly reduced with an increase in dose. (Hanlon et al., 2008) SFN is very well tolerated and did not demonstrate any toxicity even at the levels that need to be achieved for desired effectivity. All this make SFN a very powerful drug with great potential; however, further studies and trials are required to ensure effectiveness of treatment/chemoprevention.

RESVERATROL

Resveratrol (RES) (trans-3,4′,5-trihydroxystilbene) is a polyphenolic compound usually found in grapes that has shown antiaging, anti-inflammatory, and chemopreventive effects through various pathways. (Horgan et al., 2019)

RES induces cell cycle arrest and causes apoptosis of tumor cells. RES also downregulates the expression of tumor-derived nitric oxide synthase, functions as an antioxidant, and prevents DNA damage; it also reduces tumor growth. (Carter et al., 2014)

In triple-negative breast cancer cell lines, MDA-MB-231 and MDA-MB-231/PacR, RES prevents cell growth, promotes senescence, downregulates the expression of survivin, and initiates apoptosis. In promoting apoptosis, it activates caspase 7 .(Sprouse, Herbert, 2014) Moreover, RES reduces cell viability, glucose consumption, and the ATP content in MCF-7 cells; it also suppresses PFK. In this manner, RES reduces the survival and proliferation of these cells. (Gomez et al., 2013)

In breast cancer cells, RES modulates apoptotic and cell cycle machinery by regulating tumor-suppressive miRNAs. By modulating miRNAs, RES demonstrates its anticancer and anti-proliferative properties against breast cancer. (Venkatadri et al., 2016) Furthermore, in MCF-7 cells, RES enhances the expression of ASPP1, a protein activator of p53 that stimulates apoptosis. RES also upregulates BAX and p21. Its modulation of Bcl-2 inhibits cancer progression. RES increases p53 expression, reduces procaspase 8, and activates caspases 7 and 9. In addition, RES induces cell cycle arrest in the S phase and raises p-Chk2 levels. RES reduces the active form of CDK2 and blocks CDK7 activity. (Shi et al., 2011; Casanova et al., 2012)

Although resveratrol has shown great potential in breast cancer treatment by multiple pathways activity, the main issue remains its bioavailability. The chemopreventive site of resveratrol is yet to be investigated by future research and trials.

Other Natural Compound with Potential

A great deal of research is being conducted to look into more natural compounds and chemicals. As such, there is optimism that a chemopreventive potential of natural compounds will be found. Some promising results have been shown with the following compounds

Silibinin (Binienda et al., 2020)

Silibinin is a flavonolignan found in milk thistle (*Silybum marianum*). It has ability to provoke autophagic cell death in breast cancer cells by downregulating the Bcl-2 expression and upregulation of Atg12-Atg5

Table 1. Less common natural compounds and their effect

Natural compound	Effect
curcumin, resveratrol (Shindikar et al., 2016)	can treat triple negative breast cancer, reducing side effects of standard treatment
EGCG (Braicu et al., 2013)	blocks uncontrolled cell growth and can inhibit the migratory behaviour of triple-negative breast cancer
Carnosol (Al Dhaheri et al., 2014)	blocks cell cycle at G2 phase and increases ROS-dependent apoptosis and beclin-1-independent autophagy

formation and enhancing beclin-1 expression. Silibinin reduces expression of ERα causing cytotoxicity and inhibits COX-2 expression in breast cancer cells. It also increases efficacy of cisplatin and paclitaxel sensitise the chemoresistant breast cancer cells.

Rutin (Elsayed et al., 2017)

Rutin is a quercetin 3-O-β-d-rutinoside is a citrus flavonoid glycoside found in many plants including buckwheat. It promotes apoptosis in breast cancer cells and restores chemosensitivity in HER2 negative/triple negative breast cancer.

Emodin (Iwanowycz et al., 2016)

Emodin is a compound of the anthraquinone family, that can be isolated from rhubarb, buckthorn, and Japanese knotweed. It inhibits HER-2/neu tyrosine kinase activity as well as activates apoptosis through disruption of mitochondrial signalling pathway.

Rosmarinic acid (Juskowiak et al., 2018)

Rosmarinic acid is a phytocompound derived from rosemary. It inhibits breast cancer cell proliferation through reducing the COX-2 expression, AP-1 activation, and antagonises the ERK1/2 activation. Rosmarinic acid also suppresses interleukin-8 (IL-8) in the NF-κB pathway and therefore inhibits bone metastasis.

These studies are very limited, but some of the natural compounds have shown great potential in the future management/treatment and even prevention of breast cancer and would warrant more studies.

NATURAL COMPOUND IN COMBINATION WITH TRADITIONAL BREAST CANCER TREATMENT

The traditional treatment of breast cancer has recently been facing more hurdles with well-known drug toxicity and increasing drug/treatment resistance. Many adverse reactions to chemotherapy or radiotherapy became part of the treatment. However, due to the increased incidence of breast cancer cases and improvement in survival, we have to deal with more poor responses to therapy. Particularly in these cases, the natural compounds showed great potential as many of them can increase efficacy of certain

chemotherapeutics, or alter multidrug resistance in patients. Much improvement has been noted in the severity of side effects of the traditional treatment. The following table shows examples of synergic use of standard therapy and natural compound.

Table 2. Overview of natural compounds used with standard treatment

Natural compound	Standard therapy	Effect
genistein	doxorubicin	Synergic (Xue et al., 2014)
equol	tamoxifen	improves efficacy (Charalambous et al. 2013)
Pomegranate extract	tamoxifen	increases cell death and enhances inhibition of cell viability
DIM	paclitaxel	induces appoptosis (McGuire et al., 2006)
rosemary extract	tamoxifen, transtuzumab, palitaxel	increases activity (González-Vallinas et al., 2014)

CONCLUSION

A promising effect has been shown by majority of above mentioned natural compounds. Chemoresistance or multi-drug resistance has become more of an issue in recent years. The resistance towards chemotherapy can be caused by changes to ATP-binding cassette (ABC) transporters that pump anticancer drugs out of the cells. Much research has been done into chemoresistance. Multiple natural compounds showed great potential in fighting against chemoresistance and improving the response to traditional drugs, i.e., *β*-elemene, DIM. More research is yet to be conducted to assess pathways in which these compounds can affect multi-drug resistance (Xu et al., 2012).

Triple negative breast cancer is one of the most aggressive subtypes of breast cancer. It has limited treatment options due to the lack of therapeutic target. Immunotherapy has shown some great results, but more research will have to be conducted. As the targeted therapy proved to be the most effective, more research has been done into looking for potential targets in the therapy of triple negative breast cancer. A number of natural compounds have been investigated and initial results seem promising, at least for some of them.

Although this section of the chapter highlighted the most promising pathways of natural compounds, the majority of them have multiple mechanisms of action. Some of the compounds have also shown great function while in use with standard therapy. Taking all this into consideration, natural compounds have a very promising future in cancer treatment. However, bioavailability of these compounds is a common issue and will need to be addressed. Further research is yet to be done into this problem, but natural compounds are shown to have a very promising future in breast cancer management (Nobili et al., 2009).

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Chapter 3
The Molecular Mechanisms Involved in Suppressing Triple Negative Breast Cancer Using Natural Agents

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ABSTRACT

Breast cancer is an aggressive and primary cause of death among women globally. Triple negative breast cancer (TNBC) is one of the sub types of breast cancer. TNBC lacks the expression of progesterone receptor (PR), estrogen receptor (ER), and human epidermal factor 2 (HER2), which leads to poor diagnosis resulting in lack of targeted therapies. On the other hand, natural products are also cost efficient, non-toxic, and abundantly available in nature. Natural products have also been reported to exert various pharmacological activities including cardioprotective, anti-diabetic, antimicrobial, anti-inflammatory, etc. In this chapter, summarization of 12 well known natural products such as chebulinic acid, maslinic acid, apigenin, piperlongumine, Liquiritigenin, berberine, icariin, bufalin, which are targeted against TNBC through regulation of different pathways, and their mechanism are briefly explained. These natural products are already used to treat various diseases at the preclinical level and also have shown to have effective anti-tumor effect and can act as potent anti-TNBC agents.

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INTRODUCTION

Breast cancer is incessant and primary cause of death among women globally (Maurya et al., 2020). In 2018, around 2,088,849 women were affected which is about 11.6% of all cancer and among which 626,679 women died which is 6.6 percentage of all cancer deaths among women (Bray et al., 2018). Individuals in developed countries, diagnosed with breast cancer have high survival rate than breast cancer individuals in developing countries (Green and Raina, 2008). The number of breast cancer patients are two time higher in South East Asia than that of in United States. (Parkin et al., 2005). Globally, India alone accounts for 2.7% of risk of developing breast cancer along with 1.5 percentage of death risk (Monica et al., 2020). In USA, breast cancer is more observed in women whose age is in the range of 60-69 (DeSantis et al., 2019). In India, women residing in urban areas, of age between 40-45 were more prone to breast cancer, while in rural areas women of age between 60-65 were more prone to breast cancer (Chauhan et al., 2011) along with report of 26% of Northern India women diagnosed with breast cancer were below 35 years (Agarwal et al., 2007).

Breast cancer has various subtypes based on the presence or absence of progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor-2 (HER2). Triple negative breast cancer (TNBC) is a class of breast cancer where the expression of PR, ER, and over expression of HER2 is absent (Dawood, 2010). Due to absence of receptors, TNBC is aggressive in nature and often leads to poor diagnosis resulting in lack of targeted therapies (Mersin et al., 2008). TNBC contributes approximately 10 percent of all the breast cancer (De-la-Cruz-Ku et al., 2020). Individuals with TNBC has low survival rate when compared to non-TNBC (Onitilo et al., 2009). Women under the age of 40 are more prone to TNBC. There is a two-fold higher risk of TNBC in women under the age of 40 when compared to women over age of 50 (Trivers et al., 2009). It is reported that in India, TNBC is more common and has higher incidence when compared to western population (Sandhu et al., 2016). Based on differentiation stages and expression of cell marks, TNBC are classified into three sub groups which is molecular apocrine, claudin low and basal like cells. The molecular apocrine subgroup is found in progressive stages and most differentiated subgroup accounting for 0.5 to 4 percentage of TNBC with characteristics such as absence of ER, PR and HER2 with presence of androgen receptor. Basal like subgroup accounts for 75 percentage of TNBC which lacks DNA repair and overexpression of EGFR (Ma et al., 2010). Claudin subgroup of TNBC consists of poorly differentiated mesenchymal stem cells along with characteristics of CD^{44+}/CD^{24-} and upregulation of mesenchymal markers that played an important role in tumour return (Kwon, 2013). TNBC are further classified into six subtypes based on gene expression, which are basal like 1 (BL1), basal like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem like (MSL), luminal androgen receptor (LAR) which is characterized based on androgen receptor signaling (Hubalek et al., 2017; Lehmann et al., 2011)

In basal like TNBC cells, it was observed that over expression of EGFR was associated with invasion, proliferation and vascular formation of cancer (Williams et al., 2015). Tumour proliferation is regulated by MAPK pathway which when abnormally activated can provide the ability of TNBC cells to proliferate and resist apoptosis (Kim et al., 2016). Phosphatidylionsitol 3 kinase pathway (PI3K/ AKT pathway) is mostly targeted for the treatment of TNBC (Delaloge and DeForcevillie, 2017). In normal condition, PI3K pathway initiate cell cycle progression (Goncalves et al., 2018). Under abnormal condition, PI3K pathway is activated aberrantly which in turn activates cascade of response that initiates cell growth to proliferation to cell survival (Pandurangan, 2013). PI3K pathway often communicates with MAPK pathway to perform their role efficiently (Juvekar et al., 2012). PI3K pathway also initiates cell migration

(Khan et al., 2019). Other signaling pathways such as DNA repair is also dysregulated in TNBC (Murai et al., 2012). Wnt / ß- catenin signaling pathway is also targeted to treat TNBC cells. Wnt signaling pathway is found to be activated in TNBC cells which is both Wnt receptor FZD7 and Wnt co-receptor LRP6 are found to be upregulated in TNBC cells (King et al., 2012).

As TNBC lacks receptors, the cells don't respond to hormonal therapies or HER2 targeted drug therapies. So, the individuals diagnosed with TNBC are treated by chemotherapy and radiotherapy. The chemotherapeutic drugs that are used against TNBC such as adriamycin, epirubicin causes severe side effects such as hypercalcaemia, alopecia, infertility (Yip et al., 2014). When the individual is treated with surgery and radiation therapy, tissue necrosis, pericarditis, rib facture can occur as side effects (Mitra et al., 2018). Furthermore, chemotherapy leads to decrease in both white blood cells and red blood cells which results in side effects such as infection and anemia. Fatigue, diarrhea, constipation, change in skin colour and hormonal changes are some more side effects caused due to chemotherapy (Mitra et al., 2018). This urges to find an alternative therapy that can target and kill TNBC cells without causing any side effects and also is active at lower dosage (Kalimutho et al., 2015). Natural products can be used as alternative therapies for targeting TNBC cells as they are no or less toxic and cost efficient. The objective of the article is to discuss various natural products and their level of efficiency against TNBC cells.

NATURAL PRODUCTS

Natural products as therapeutic drug has more advantageous than the convention therapy. They are less toxic, cost efficient and the source is abundantly available. Natural products are used for various disorders and are classified into two broad sub groups which is flavonoid and alkaloids (Laraia et al., 2017). The natural products have already been used as therapeutic drugs and proven to be efficient as antidiabetic (Binh et al., 2020; Aziz et al., 2017), cardioprotective (Patrignani et al., 2021; Hemmati et al., 2017), antimicrobial (Józsa et al., 2020; Pandurangan et al., 2016), anti-inflammatory (Saied et al., 2020), hepatoprotective (Meng et al., 2020; Tzankova et al., 2017), nephroprotective (Mahmod et al., 2020; Giribabu et al., 2017), and neuroprotective (Wei et al., 2020). Few natural products that are targeted against TNBC are listed below (Fig. 1).

Chebulinic acid

Chebulinic acid is a hydrolysable polyphonol which is present more in medicinal plants such as phyllanthus emblica, Terminalia arborea and Terminalia chebula (Yi et al., 2009). Chebulinic acid is also present abundantly in plant foods which is used in traditional Indian medicine, such as "triphala" that has dried fruits in powdered form of three different plants whose major constituent is chebulinic acid (Shanmuganathan et al., 2018). Shi et al., (2008) reported that pure form of chebulinic acid inhibits cancer cell growth both *in-vitro* and *in-vivo*. The cytotoxicity of chebulinic acid induced DNA damage and inhibited DNA gyrase activity (Khan et al., 2018). Chebulinic acid also have anti-angiogenic effect (Lu et al., 2012), anti-tumour effect against colorectal carcinoma and retinoblastoma cell lines (Reddy et al., 2009) and anti-migration effect which inhibits migration of smooth muscle cells (Song et al., 2017). Chebulinic acid targets SOD1 in cancer therapy which is found upregulated in most of the cancer (Papa et al., 2014) and found in higher level in breast cancer and lung cancer individuals (Gomez et al., 2019). Inhibition of SOD1 induces apoptosis in cancer cells (Li et la., 2019).

Sharma et al., (2020) reported that increased level of Chebulinic acid induced cell death in a caspase independent manner, in MDA-MB-231 breast cancer cells and also reduced proliferative and metastatic characteristics of triple negative breast cancer. Chebulinic acid inhibited MMP9, reduced the expression of N-cadherin and negatively regulated mesenchymal characteristics of MDA-MB-231 cells. Chebulinic acid promoted S phase growth arrest. Chebulinic acid reduced the activity of SOD1 inducing cell death. Downregulation of SOD1 enhances cellular ROS leading to induction of autophagy. The ability of Chebulinic acid to promote apoptosis in triple negative breast cancer cells can result in additional benefit when used with chemotherapeutic drugs that leads to reduced toxicity, reduced does of chemotherapeutic drugs resulting in lower level of side effects and reduced overall cost.

Maslinic acid

Olives which is easily available and safe for human body, is associated with low occurrence of Breast cancer (Bosetti et al., 2003). Olive also reduced the risk of coronary disease (Keys et al., 1984). Maslinic acid, a phytochemical compound present in the skin of olives Possess efficient anticancer activity (Reyes et al., 2006). Maslinic acid is also cardioprotective (Nieto et al., 2013), anti-inflammatory (Márquez Martín et al., 2006), anti-oxidant (Montilla et al., 2003), and anti-hypertensive (Rodriguez-Rodriguez et al., 2006). In adenoid cystic carcinoma, Maslinic acid altered Ca2p that evoked p28 signaling pathway resulting in apoptosis (Wu et al., 2011). Maslinic acid enhanced caspase dependent apoptosis pathway that results in inhibition of tumour growth in pancreatic cancer (Li et al., 2010). Maslinic acid showed proapoptotic in B16F10 Melanoma cell lines (Parra et al., 2011).

Jain et al., (2020) reported that Maslinic acid inhibited cell proliferation in MDA-MB-468 and MDA-MB-231cells within 24hlurs of treatment with concentration about 25muM. Maslinic acid also revoked migratory and adhesive ability of cancer cells. Maslinic acid induced G0/G1 cell cycle arrest. Maslinic acid increased the expression of CDK4 thus arresting the cells in G1 phase and decreased the expression of CDK 2. It also increased the expression of Bax and decreased the expression of Bcl-2 which results in increased Bax/Bcl2 ratio which makes cells susceptible to apoptosis. MAPK/ERK is a supporting factor for cell survival as well as functions as pro apoptotic factor. Maslinic acid also downregulates survivin confirming the mechanism of apoptotic action which was caspase 3 independent pathway involving MAPK/ERK signaling mechanisms. Also, the loss of electro-potential gradient of mitochondria triggered the caspase independent process and maslinic acid inhibited ROS production resulting in decreased cell proliferation rate leading to cell death.

Apigenin

Apigenin, a dietary flavone found highly in celery and parsley. It has proven to be a potential sensitizer to doxorubicin in breast cancer (Seo et al., 2017). Apigenin has the ability to induce intrinsic apoptotic pathway involving caspase 9 dependent mechanism (Seo et al., 2015). Sugar bound glycoside form of Apigenin is found in plants (Jiang et al., 2016) that has shown anti-inflammatory activity (Hostetler et al., 2012). Apigenin has higher affinity to heterologous ribonuclear protein A2/B1 (hnRNPA2) which is an RNA binding protein that regulates mRNA stability and alternate splicing (Glisovic et al., 2008) and it is an oncogenic driver which is found highly upregulated in breast cancer (Klinge et al., 2019). Doxorubicin causes cell death through DNA damage by breaking double strand that leads to phosphorylation of histone H2AX (Rogakou et al., 1998). DNA damage activates caspase 9 dependent intrinsic pathway

(Norbury et al., 2004) which in turn activates caspase 3 results in cell death (Yang et al., 2001). When failed to activate caspase 3 the cancer cell acquires resistant to doxorubicin (Hembruff et al., 2008). Over expression of ATP binding cassette (ABC) efflux transporters such as ABCC1, ABCC4, ABCB1 and ABCG2 contributes to doxorubicin in triple negative breast cancer. (Gao et al., 2016; Kochel et al., 2017).

Sudhakaran et al., (2020) reported that, Apigenin increased cytotoxicity of doxorubicin causing cell death. Apigenin reduced growth and viability of MDA-MB-231cells. Apigenin also reduced the expression of ABCC4 but did not show any effect on SLC22A16 doxorubicin influx transporter. Reduction of ABCC4 and expression of ABCG2 mRNA in triple negative breast cancer required hnRNPA2, while expression of ABCB1 and ABCC1 was hnRNPA2 independent. Apigenin also reduced HIF-1α level in MD-AMB-231 cells. Thus, hnRNPA2 plays an important role in Apigenin mediated sensitization of MDA-MB-231cells, a TNBC to doxorubicin that enhances the activation of intrinsic apoptotic pathway by triggering caspase 3 activity.

Piperlongumine

Piperlongumine, a bioactive alkaloid which is present in fruit of long pepper plant is commonly used as spice and traditional medicine to treat various ailments (Prasad et al., 2016) and selectively kills breast cancer cells (Jin et al., 2014). Cancer cells are sensitive to oxidative stress as they have more ROS (Wang et al., 2008) and the cytotoxicity activity of Piperlongumine is reason for the oxidative stress due to increased level of hydrogen peroxide in Piperlongumine treated cancer cell (Huang et al., 2016). Piperlongumine inhibits JAK2- STAT3 pathways (Chen et al., 2019), NF-κB (Niu et al., 2015), PI3K/Akt signaling pathway (Shrivastava et al., 2014) and activates proapoptotic C/EBP homologous protein (Jin et al., 2014).The loss of epithelial properties such as cellular adhesion and acquisition of mesenchymal Properties which results in motile and invasive cells is known as epithelial to mesenchymal transition which migrates to distant tissues and develop into new tumour with greater genetic and phenotypic heterogeneity (Almendro et al., 2014). Expression of matrix metalloproteineases (MMP) upregulates EMT activation, invasion and metastasis in breast cancer cells (Radisky et al., 2010).

Delaney et al., (2020) reported that, Piperlongumine treated MDA-MB-231 TNBC cells showed suppressed metastatic activity both *in-vitro* and *in-vivo* and altered the expression of EMT. Piperlongumine also inhibited migration and invasion of MDA-MB-231 cells. Piperlongumine at low concentration suppressed the expression of MMP2 and MMP9 which aids cancer cells to invade surrounding tissues. In piperlongumine treated MDA-MB-231 cancer cell, the expression of EMT promoting transcription factor ZEB1 and slug was decreased along with Increased expression of E-cadherin which is an adhesion molecule and an epithelial marker. Piperlongumine also suppress TGF beta signaling pathway which plays an important role in stimulation of EMT, upregulation of MMP2 and MMP9 and cancer progression. IL-6 which is responsible for aggressive nature of mda-mb-231 cancer cells and induces EMT is expressed low in piperlongumine treated cancer cell due to decreased expression of ZEB1, the regulator of IL-6. The decreased expression of metastatic promoting such as IL-6, MMP2, MMP9 and Increased expression of metastasis suppressing molecule such as E-cadherin was dependent on piperlongumine. Thus, the anti-metastatic effect of piperlongumine on TNBC cells make them more sensitive to chemotherapeutic and ionizing agents.

Liquiritigenin

Liquiritigenin, extracted from Glycyrrhizae radix, is a natural flavonoid which exhibits various biological activity such as anti-oxidant (Zhang et al., 2020), anti-inflammatory (Lee et al., 2020), and anti tumour activity (Wang et al., 2014). Liquiritigenin has inhibited cell proliferation, invasion, migration and epithelial to mesenchymal transition in colorectal cancer cells (Meng et al., 2019). Liquiritigenin also reduces angiogenesis, tumor growth (Liu et al., 2011) and also enhances cisplatin mediated inhibitory effect (Shi et al., 2015). BRAC1 protein is a tumour suppressor Which is important for DNA damage repair and transcriptional regulation (Ali et al., 2017). BRAC1 mutation or promoter methylation is closely associated with high risk of sporadic breast cancer (Su et al., 2018) especially TNBC (Zhu et al., 2015). When BRAC1 is suppressed, it resulted in malignant cell behavior leading to reduced apoptosis, faster cell proliferation, migration and invasion (Romagnolo et al., 2015). Therefore, inhibition of BRAC1 mutation or promoter methylation can prevent occurrence of breast cancer.

Liang et al., (2020) reported that, liquiritigenin decreased cell viability and colony formation of MDA-MB-231 and BT549 cells at high concentration. Liquiritigenin inhibited cell proliferation, invasion, migration and increased apoptosis and caspase 3 activity in MDA-MB-231 and BT549 triple negative breast cancer cells. Liquiritigenin increased the mRNA and protein expression of BRAC1 and upregulated p21 and growth arrest and DNA damage inducible 45 alpha (GADD45A) gene and decreased cellular DNA methyltransferase (DNMT) activity along with decreased expression of DNMT1, DNMT3a and DNMT3b which is alone responsible for inactivation of BRAC1 and also reduced BRAC1 promoter methylation. Liquiritigenin treated breast cancer cell upregulated E-cadherin as well as downregulated N-cadherin and MMP-9. Thus, liquiritigenin downregulates DNMT and enhance BRAC1 protein expression aiding in treatment of TNBC cells.

Berberine

Berberine, an organic heteropentacyclic compound and isoquinoline alkaloid extracted from *coptis chinensis* and *cortex phellodendri chinensis*. It is widely used to treat diarrhea caused due to gastroenteritis. Berberine is characterized as odourless yellow crystalline powder with alkaloid bitterness and is poorly soluble in water (Feng et al., 2019). Berberine performs various biological activity such as anti-pathogenic (Kong et al., 2012), anti-diabetic (Chang et al., 2015), cerebrovascular protection (Wang et al., 2012), blood lipid regulation (Dong et al., 2013) and importantly acts as anti-inflammatory (Zhang et al., 2014). Berberine has also shown anti-tumor effect (Li et al., 2018) such as inducing apoptosis, autophagy (Wang et al., 2010), ROS formation (Xie et al., 2015) and cell cycle arrest (Zhuo et al., 2017). Berberine also regulates NLRP3 inflammasome pathway (Jiang et al., 2017). Inflammation is highly associates with tumor initiation, progression, metastasis and interaction with environment (Zitvogel et al., 2012). Pro-inflammatory mediators such as cytokines, chemokines, transcriptional factor from cancer cells play an important role in regulating signaling pathway and processes involved in oncogenesis. Thus, regulating inflammatory pathway can aid in prevention of triple negative breast cancer (Hussain et al., 2007). The NOD like receptor family pyrin containing domain 3 (NLRP3) which consists of NLRP3 oligomers and apoptosis associated speck like (ASC) adapter protein which plays an important role in innate immune pathway by activation of caspase 1 which in turn activates IL-1β and IL-18 resulting in induction of pyroptosis and malignant transformation (Kantono et al., 2017). It is also involved in the development

of various inflammatory disorders such as Inflammatory bowel disease (Nunes et al., 2013), pancreatitis (Antonucci et al., 2015) and increase the risk of cancer (Karki et al., 2017).

Yao et al., (2019) reported that, berberine reduced the cell viability with increase in LDH leakage indicating the cytotoxicity level of berberine in MDA-MB-231 cells within 48 hours. Berberine also inhibited cell migration and colony formation in MDA-MB-231. The Secretion of pro Inflammatory cytokines such as IL-1alpha, IL-1β, IL-6 and TNF- alpha was reduced in berberine treated MDA-MB-231 cells resulting in inhibition of maturation of cells. Berberine also downregulated the expression of mRNA and proteins involved in inflammasome cascade. P2X7 which is essential for cell triggering NLRP3 inflammasome pathway and cancer cell invasion associated with metastasis is downregulated in berberine treated MDA-MB231 triple negative breast cancer cells. In Berberine treated MDA-MB-231 cells, the expression of mRNA and protein of nod like receptor protein (NLRP3), ASC, and pro caspase 1 were downregulated along with decreased activity of caspase 1 and expression of IL-1ß and IL-18 at low level. Thus, berberine acts as effective anti-tumor agent by preventing TNBC proliferation and metastasis through inhibition of NLRP3 inflammasome pathway.

Icariin

Icariin which is extracted from Herba epimedii, is a prenylated flavonol glycoside (Pan et al., 2007). Icariin has shown numerous pharmacological action which includes antidepressant, cardiovascular protective, osteogenic and immunomodulatory actions (Xu et al., 2007). Icariin has also proven to be an effective NF-κB inhibitor to improve fanconi anemia hematopoietic stem cell function (Su et al., 2018). Icariin also have shown anticancer activity in gastric, lung and prostate cancer cells (Geng et al., 2014). NF-κB is an important B cell specific transcription factor that regulates cell proliferation, inhibits apoptosis, increases cell migration and invasion and also regulates metastasis and angiogenesis (Zhang et al., 2017). Oxidative stress, DNA damage results die to activation of NF- Kappa B (Karin et al., 2005). The activity of NF-κB is observed in various types of cancer including breast cancer, colorectal cancer (Staudt et al., 2010). NF-κB plays an important role in cancer development, on activation of NF-κB, it induces metastatic activation through epithelial to mesenchymal transition (Karagiannis et al., 2017). NF-κB enchants cancer cell migration and invasion through induction of MMP2 and MMP9 (Huang et al., 2001). NF- κB also regulates proliferation of regulatory T cells and transcription of PD-L1 (Maeda et al., 2018). Thus, inhibiting NF-kappa B prevent TNBC occurrence.

Song et al., (2020) reported that, icariin inhibited cell proliferation and viability of MDAMB231 and murine breast cancer 41T cell line in time and dose dependent manner. Icariin caused cell death in MDA-MB-231 and 41T cells by upregulating Bax along with suppression of Bcl2 and ROS formation through alteration in mitochondrial membrane potential, leading to activation of mitochondrial mediated apoptotic pathway. Icariin treated MDA-MB-231 cells inhibited NF-kappa B pathway by upregulation of SIRT6 which is a specific histone H3 lysine 9 (H3k9) deacetylase and aid in gene suppression that leads to inhibition of metastasis and invasion. Icariin also enhanced the expression of E-cadherin. Thus, icariin prevents TNBC cell proliferation through inhibition of NF-κB signaling pathway and inducing mitochondrial mediated apoptosis.

Curcumol

Curcumol, a natural compound which has various therapeutic and beneficial effect and is extracted from curcuma longa plant (Li et al.,2019). The anti-tumour activity is a contribution of various other activities exerted by Curcumol such as anti-inflammatory, anti-oxidant, pro apoptotic, anti-cell adhesion activity and its role in cell cycle arrest (Wei et al., 2019; Li et al., 2018). Curcumol also inhibits the migration and invasion activity of breast cancer cell by regulating NF-kB dependent expression of MMP9 by blocking JNK/AKT signaling pathway (Ning et al., 2016). Curcumol treated MDA-MB-231 cells inhibited proliferation and induced apoptosis by activation of tumor suppressor protein p73 and pro apoptotic protein PUMA (Huang et al., 2017). Curcumol also deactivated pro survival signaling such as ERK and Akt which was induced pro apoptotic effect in non-small cell lung cancer and nasopharyngeal carcinoma (Cai et al., 2017). Tumor cells during their metastasis, they detach from their primary site, invade blood vessels and proliferate in distal organs (Hu et al., 2020). On losing interaction with extracellular matrix or neighboring cells, the tumor cells might undergo anchorage dependent programmed cell death and the process is referred as anoikis (Ishikawa et al., 2015). Cytoskeleton disruption accompanied by cell matrix dissociation, induces anoikis which releases pro apoptotic factor such as Bim or death factors such as Fas from sequestered state (Paoli et al., 2013). Tumor cells can acquire resistance to anoikis either by gene mutation or over expression of anti-apoptotic proteins (Kim et al., 2012). Anoikis resistance of tumor cells help them to escape from apoptosis and allows anchorage independent cell growth (Paoli et al., 2013). Thus, anoikis resistance is one of the important features of cancer metastasis (Wang et al., 2009) and also it upregulates genes involved in epithelial to mesenchymal transition such as Zeb1 and Skp2 which acts as indicator of anoikis resistance (Takeyama et al., 2010). Skp2 is a F-box protein and E3 ubiquitin ligase (Zhang et al., 2016), besides anoikis resistance, it also promotes invasion and metastasis in several cancer types (Zhang et al., 2018). YAP1 could regulate cell ploidy and tumorigenesis through Skp2 and affect the anoikis process in various cancer types (Zhang et al., 2017).

Recently, Li et al., (2020) reported that Curcumol suppressed the viability of attached and suspended IV2-1 TNBC cells. Curcumol inhibited cell migration and invasion of TNBC cells and the expression of genes related to EMT such as vimentin, Zeb1 was decreased. Curcumol also induced apoptosis in IV2-1 cells. In IV 2-1 cells, expression of Skp2 was high and Bim was low on suspension culture condition. When the IV2-1 cells were treated with Curcumol, it inhibited the anoikis resistance by downregulating Skp2 and downstream effectors in suspended condition. Curcumol can inhibit Skp2 on both mRNA and protein level through regulation of YAP1/TEAD4 signaling. Curcumol treated IV2-1 cells promoted phosphorylation of YAP1 and decreased the expression of YAP1 protein. Thus, Curcumol is an effective Skp2 targeted therapy that suppress anoikis resistance and metastasis and prevented tumor development in TNBC cells.

Celastrol

Celastrol which is found in the roots of a Chinese herb *Tripterygyium wilfordi* and is a natural phytochemical that acts as anti-cancer agent in various cancer types by exerting proapoptotic, anti-angiogenic, anti-metastatic and anti-inflammatory (Kashyap et al., 2018). Anti-metastatic ability of celastrol was observed in ovarian cancer (Wang et al., 2017), chondrosarcoma (Wu et al., 2017) and osteosarcoma (Yu et al., 2016). Celastrol suppress the mTOR pathway and inhibited breast cancer cell growth, both *in vivo* and *in vitro* (Li et al., 2018). Celastrol also Inhibits the growth of breast cancer cell by regulating

estrogen receptor alpha (Jang et al., 2011). Celastrol induces apoptosis and increase the level of ROS formation and Inhibits cell viability in breat cancer cells (Kim et al., 2013). Celastrol also induce ROS production and mitochondrial dysfunction and inactivates PI3K pathway and protein kinase B pathway resulting in apoptosis of TNBC cells (Shrivastava et al., 2015). Interleukin-6 which is a multifunctional cytokine that controls cells growth, angiogenesis, and other progression in various cancer types (Taher et al., 2018). IL-6 also serves as negative prognosticator in breast cancer cells (Knüpfer et al., 2007). IL-6 is important for the growth of TNBC cells and is found in high level (Hartman et al., 2013). NF-kB regulates the expression of IL-6 through binding sites within the IL-6 promoter area and this mechanism plays an important role in breast cancer progression (Okamoto et al., 2016). Inhibition of IL-6 can reduce the metastatic capacity of cancer cells (Jayatilaka et al., 2017) and cell viability, colony formation can also be inhibited (Fu et al., 2018). Inhibition of NF-kB/IL-6 signaling pathway can suppress migration and angiogenesis of TNBC cells (Liang et al., 2020).

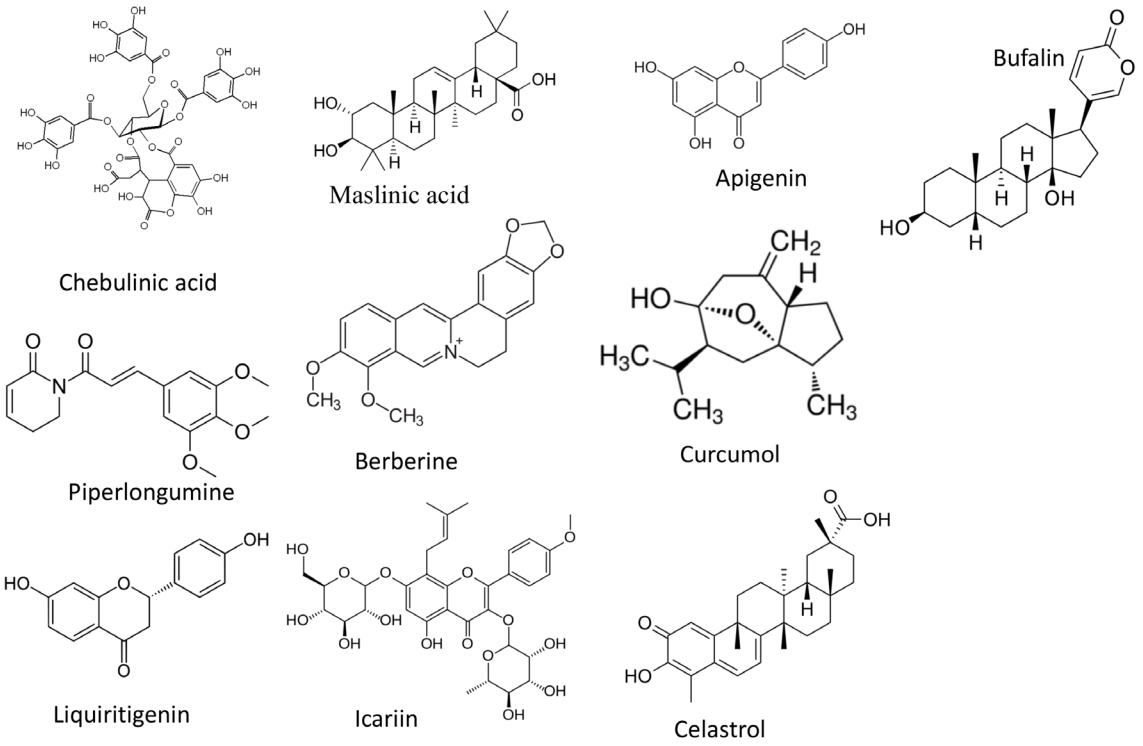
Yan et al., (2020) reported that Celastrol at the concentration of 2 or 5 μM inhibited cell viability of MDA-MB-231 and MDA-MB-468 TNBC cells within 24 hours. Celastrol also suppressed the migration and invasion of TNBC cells with its anti-metastatic ability. IL-6 is expressed in high level in breast cancer cells and it's is found to be higher in MDA-MB-231 compared to MDA-MB-468 TNBC cells. Celastrol decreased the expression of IL-6 and thus blocked migration and invasion of TNBC cells. Celastrol induced accumulation of IκB-α through phosphorylation of IKB-alpha that leads to reduction of p65 which results in inhibition of activation of NF-κB signaling pathway, due to which the expression of IL-6 was decreased. Thus, Celastrol can act as novel agent to treat TNBC by inhibiting migration and invasion through blocking NF-κB/IL-6 signaling pathway.

Bufalin

Bufalin is a cardiotonic steroid which is obtained from the venom of toad that exerts various pharmacological functions such as blood pressure stimulation, pain relief and anti-inflammation (Calderón-Montaño et al., 2014). Toad skin and toad skin extract are used as traditional medicine in China and also used in cancer treatment (Qi et al., 2010). Bufalin is also used to treat various cancer types including breast cancer (Lan et al., 2019). Bufalin can effectively inhibit cell proliferation, metastasis, invasion and induced apoptosis and promote cell cycle arrest in cancer cells (Wang et al., 2018; Feng et al., 2018). And also, bufalin exerts their functions without causing any side effects (Takai et al., 2012). The normal cell markers are present in a small portion in cancer cells which is known as cancer stem cells [CSCs] (Creighton et al., 2009). The cancer stem cells (CSCs) possess low sensitivity and higher resistance towards drug and irradiation (Pavlopoulou et al., 2016). Cancer stem cells are the reason for recurrence and metastasis of cancer cells (Peitzsch et al., 2017). Therefore, targeting CSCs and non- CSCs can effectively inhibit cancer cell growth. Y-box 2 (SOX2) is a transcription factor sex determining region which is found to be highly expressed in TNBC cells which results in poorer differentiation and less survival rate of individuals (Yao et al., 2018). SOX2 can acts as tumor promoter by regulating cell proliferation and metastasis (Liu et al., 2018). The expression of octamer binding transcription factor 4 (OCT4) is also found cancer cell and is associated with poorer prognosis of TNBC post-surgery (Zhang et al., 2018).

Chen et al., (2020) reported that bufalin promoted G2/M cell cycle arrest and induced apoptosis in MDA-MB-231 and HCC1937 TNBC cells. Bufalin also induced apoptosis in TNBC cells. Bufalin treated TNBC cells inhibited cell proliferation by promoting G2/S cell cycle arrest and decreasing the entry of cells into G1/G0 phase. Bufalin treated MDA-MB-231 and HCC1937 TNBC cells had reduced ability

Figure 1.



to form spheroids. Bufalin also reduced the expression of SOX2 and OCT4 at mRNA level. Bufalin also reduced the self-renewal ability of TNBC cells. Thus, bufalin can acts as therapeutic agent for TNBC through SOX2/OCT4 pathway.

CONCLUSION

Triple negative breast cancer is one other destructive form that is difficult to treat due to the lack of key receptors. There are lot of research is undergoing by researchers from all over the world. Natural products are an alternative medicine that is available cheap and potent. We here in report that natural products such as Bufalin, Curcumol, Berberine, Celastrol, chebulinic acid, maslinic acid, apigenin, piperlongumine, Liquiritigenin, and icariin were potentially inhibiting the proliferation of TNBC cells. In addition, they try to inhibit the key signaling mechanism and induce apoptosis. We conclude that, these natural products are effective in preclinical level and it should be tested in clinical setting.

Table 1. List of natural products and their mechanism of action against TNBC

S.No	Name of the natural product	Cancer model	Mechanism of action	References
1.	Chebulinic acid	MDA-MB-231 TNBC cells.	• Induced cell death in a caspase dependent manner. • Reduced proliferation and metastatic. • Reduced MMP9, N-cadherin expression. • S phase cell cycle arrest. • Downregulated SOD1 and induced autophagy.	Sharma et al., 2020.
2.	Maslinic acid	MDA-MB-231 TNBC cells and MDA-MB-468 TNBC cells.	• Inhibits cell proliferation • Inhibits migration and suppresses adhesive ability • Induce G0/G1 cell cycle arrest • Increased expression of CDK4, Bax • Decreased the expression of CDK2, Bcl2 and induce apoptosis which is caspase 3 independent pathway involving MAPK/ERK signaling mechanism.	Jain et al., 2020.
3.	Apigenin	MDA-MB-231 TNBC cells.	• Increased cytotoxicity of doxorubicin • Reduced the growth and viability of cells • Reduced the expression of ABCC4 • Reduced HIF-alpha protein level • Enhanced the activation of intrinsic apoptotic pathway by triggering caspase 3 activity	Sudhakaran et al., 2020.
4.	Piperlongumine	MDA-MB-231 TNBC cells.	• Suppresses the metastatic activity of TNBC cells. • Alter the expression of EMT • Inhibited migration and invasion of cells • Suppresses the expression of MMP2 and MMP9 • Decreased the expression of ZEB1 and slug and increased E-cadherin expression and also suppressed TGF beta signaling pathway • IL-6 was expressed at lower level	Delaney et al., 2020.
5.	Liquiritigenin	MDA-MB-231 TNBC cells and BT549 cells.	• Decreased cell viability and colony formation • Inhibited cell proliferation, invasion, migration and increased apoptosis and caspase 3 activity • Increased the expression of BRAC1 and upregulates p21 and GADD45 • Decreased DNMT activity • Upregulates E-cadherin and downregulates N-cadherin and MMP9	Liang et al., 2020.
6.	Berberine	MDA-MB-231 TNBC cells.	• Reduced cell viability and induced high cytotoxicity level • Inhibited cell migration and colony formation • Downregulated T2X7 expression • Downregulated the expression of NLRP3, ASC and pro caspase 1 • IL-1 beta and IL-18 was expressed at lower level.	Yao et al., 2019.
7.	Icariin	MDA-MB-231 TNBC cells and murine breast cancer 41T cell line.	• Inhibited cell proliferation and viability • Upregulated Bax and suppressed Bcl2 and ROS formation leading to activation of mitochondrial mediated apoptotic pathway • Inhibited NF-kappaB pathway by upregulating SIRT6 leading to inhibition of metastasis and invasion of cells • Enhanced the expression of E-cadherin	Song et al., 2020.
8.	Curcumol	IV2-1 TNBC cells.	• Suppress the viability of attached and suspended cells • Inhibited cell migration and invasion and expression of genes related to EMT • Induced apoptosis • Inhibited anoikis resistance of cell by downregulating Skp2 • Inhibited Skp2 through regulation of YAP1/TEAD4 signaling.	Li et al., 2020
9.	Celastrol	MDA-MB231 cells and MDA-MB-468 cells.	• Inhibited cell viability of cancer cells within 24 hours • Suppress the migration and invasion of cells • Decreased the expression of IL-6 • Induced accumulation of IKB-alpha leading to reduction of p65 level which inhibited the activation of NF-kB signaling pathway.	Yan et al., 2020.
10.	Bufalin	MDA-MB-231 cells and HCC1937 TNBC cells.	• Promoted G2/M cell cycle arrest • Induced apoptosis • Inhibited cell proliferation by promoting G2/S cell cycle arrest and decreasing the entry of cells in to G1/G0 phase • Reduced the expression of SOX2 and OCT4 • Reduced the self-renewal and spheroids forming ability.	Chen et al., 2020.

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Chapter 4
Natural Products Application and Combination Therapy in Colorectal Cancer Treatment

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ABSTRACT

Colorectal cancer (CRC) is one of the common types of cancer affecting humans. The treatment of CRC involves surgery and chemotherapy. CRC treatment using the conventional chemotherapeutics has a negative burden on the patient's health as a result of high toxicity, occurrence of side effects, and drug resistance. Therefore, there is a pressing need to discover more effective and efficient approaches and drugs for treating CRC. This chapter will shed more light on the conventional treatment of colorectal cancer. This chapter discusses the natural products that have anti-CRC effects such as the polyphenols (curcumin, resveratrol), irinotecan, Ganoderma lucidum, cannabinoids, flavonoids, and terpenes. Furthermore, this chapter also highlights the importance of combination chemotherapy (conventional therapy and natural products) in treating CRC. It is believed that this area of research could be a promising approach to minimize side effects and drug resistance linked to the conventional chemotherapy.

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INTRODUCTION

Colorectal cancer (CRC) is the fourth leading cause of cancer-related deaths worldwide and the third most occurring type of cancer (followed after lung and breast) (Ferlay *et al.,* 2015). Statistics from GLOBOCAN in 2012 revealed 1.6 million new cases of CRC and about 694,000 deaths were recorded annually from CRC (Ferlay *et al.,* 2015). CRC occurrence and progression are dependent on multiple factors ranging from age, gender, family history, region and personal history (Peng *et al.,* 2018; Shen *et al.,* 2018). Lichtenstein et al. (2000) reported that CRC is susceptible to inheritance with an estimation risk of 12-35% linked to genetic factors. CRC development can be closely linked to genetic changes which include microsatellite instability (MSI), *KRAS, BRAS* and *PIK3CA* mutations (Ogino *et al.,* 2011). Wasserman and colleagues revealed that loss of SMAD4 is a marker for CRC patients (Wasserman *et al.,* 2019). Other studies have revealed that obesity and smoking are risk factors for CRC (Ogino *et al.,* 2013; Suzuki *et al.,* 2014). However, the risk of CRC can be minimal with proper dietary pattern and lifestyle (Peters *et al.,* 2015). Jeffrey and Williams (2005) reported that carcinogens challenge daily DNA repair mechanism through multiple ways which include diet. Studies have shown that calcium intake is inversely correlated to CRC risk (Zhang *et al.,* 2016; Yang *et al.,* 2019). Calcium helps in modulating T cell function which in turn helps in the preventing CRC (Zhang *et al.,* 2016). Jayasekara and colleagues revealed that alcohol intake increased the risk of CRC by causing *KRAS* mutation (Jayasekara *et al.,* 2017).

Natural products have manifested great biological activities against tumor development even in high-risk population. For instance, Yuan and colleagues revealed that in a high-risk population of breast cancer among Chinese women as a result of genetic disposition, intake of green tea leads to a risk reduction for breast cancer in the population (Yuan *et al.,* 2005). In a similar study, it was reported that the consumption of decaffeinated green tea extracts reduced the risk of breast cancer (Samavat *et al.,* 2017). Therefore, in this chapter, we focus on the application of natural products and combination therapy in colorectal cancer treatment.

CONVENTIONAL TREATMENT OF COLORECTAL CANCER

Conventional treatment of CRC is basically surgery and chemotherapy. At early stage of CRC, surgical resection is commonly used to remove the tumors. Metastatic form of CRC occurs as a result of late detection of colorectal tumor, fast development of colorectal tumor and partial surgical removal of colorectal tumors. In the metastatic form of CRC, the principal therapeutic approach is chemotherapy. The classification of chemotherapeutic agents is based on their actions on DNA replication inhibitors and mitosis inhibitors (Lindskog *et al.,* 2014). Chemotherapeutic drugs include alkylating agents, antitumor antibiotics, antimetabolites and so on. The commonly used chemotherapeutic agents to combat CRC are the oxaliplatin (platinum derivatives), capecitamine, 5-fluorouracil (5-FU) (antimetabolites) and irinotecan. The front-line chemotherapeutic treatment of advanced CRC involves the use of 5-FU with leucovorin singly or in combination with oxaliplatin (de Gramont *et al.,* 2000). Similarly, Douillard et al. (2000) also revealed from their experiment that the chemotherapeutic treatment of metastatic CRC involves 5-FU or the combination of 5-FU with irinotecan. A possible way of improving the treatment and delaying the adverse effects is the use of combinational therapy (Bastos *et al.,* 2010). Drug resistance and toxicity are associated with the use of chemotherapy. Combination therapy manifests a better result when compared to monotherapy (Nautiyal *et al.,* 2011). Chemotherapeutic drugs affect both

tumor cells and healthy cells. This might lead to serious side effects in CRC patients. Chemotherapeutic drugs destroy not only the tumor cells, but also erythrocytes, leucocytes, and hair follicle cells (Gerber, 2008). Side effects differ depending on chemotherapeutic drugs. Side effects associated with 5-FU include vomiting, nausea, diarrhea, headaches, skin pruritus, myelosuppression, anemia, cardiotoxicity, anxiety and hair loss (O'Connor, 2015). Side effects associated with oxaliplatin include neuropathy, loss of hearing, nausea, vomiting, neutropenia, low level of potassium in the body, and renal failure (Ehrsson *et al.,* 2002). As a result of the numerous adverse side effects caused by chemotherapeutic drugs, drug's efficacy is limited. Therefore, this chapter reviews the effectiveness of natural products in treating CRC and also the combination of natural products with the conventional chemotherapeutics in treating CRC. This can improve the quality of life of CRC patients and also improve the efficacy of CRC treatment.

NATURAL PRODUCTS IN COLORECTAL CANCER THERAPY

Natural products are bioactive substances present in plants (carotenoids, flavonoids, terpenoids), mushrooms and bacteria. Natural products might exhibit chemopreventive effects on DNA (Nobili *et al.,* 2009). Natural products are the origin of many of the current anti-cancer drugs, such as irinotecan, vincristine and paclitaxel, and products derived from plants. Newman and Cragg (2016) reported that about 50% of the anti-cancer drugs are directly or indirectly linked to natural products. Pan and colleagues reported that some natural compounds can regulate signaling pathways and control gene expressions associated with cell differentiation and apoptosis (Pan *et al.* 2011). Although, natural products are beneficial due to their pharmacological activities. However, some products can be toxic and have an adverse effect on the body. The use of conventional chemotherapy in colorectal cancer has revealed some limitations and current research includes using combined therapy which involves the use of conventional chemotherapeutics together with a natural compound or multiple natural products. Singh and colleagues reported that the use of combined therapy is more effective than the conventional chemotherapy (Singh *et al.,* 2013). Housman et al. (2014) reported that the use of combined therapy, that includes conventional therapeutics and a natural product, reduces the resistance to anticancer drugs because the combined therapy targets many metabolic pathways. Natural products can be classified according to their function, chemical structures and pathway of action. Considering chemical structures, natural products can be classified as terpenes, carotenoids, phenolic compounds (flavonoids, tannins, coumarins resveratrol), alkaloids, organosulphates and polysaccharides. Natural products have provided a novel approach to cancer therapy. The paragraphs below summarized natural products studies relating to CRC.

Ganoderma lucidum

Ganoderma lucidum (GL) is one of the mushrooms used in Asian countries, generally called 'Reishi' in Japan and 'Ling Zhi' in China. Accumulating evidence revealed that GL has a remarkable benefit in preventing and treating different types of cancer, especially colorectal cancer (Lu *et al.,* 2001). GL has anti-inflammatory and immunomodulating effects (Chang *et al*., 2014). The bioactive components in GL with anti-tumor activity are two groups of compounds which are polysaccharide (GLP) and lanostaine-type triterpene (GLT). The polysaccharides contain glycan and glyprotein while the triterpene contains ganoderic acid, ganoderic alcohol with its derivative (Boh, 2013). Some studies revealed that the main function of the polysaccharide in GL is to activate neutrophil, dendritic cell, lymphocytes and

the natural killer cell (Zhu *et al.,* 2007; Hua *et al.,* 2007). Some other studies also revealed that GLP has anti-inflammatory, hypoglycemic and anti-tumor effects and its use leads to reduction in oxidative DNA damage and inhibition of the formation of reactive oxygen species (ROS) (Sliva, 2003; Chang *et al.,* 2014). Studies revealed that triterpene component of GL aid the inhibition of farnesyl protein transferase activity and also inhibit 5α-reductase activity (Lee *et al.,* 1998; Liu *et al.,* 2006), GLT also suppresses the proliferation of HT-29 colon carcinoma cells. In a paper by Lu and group, mice were injected with dimethyhydrazine (DMH) for a period of 10weeks to induce colon cancer. After the development of colon cancer, rats were then fed with water-soluble fraction of GL for 10 weeks. The early changes seen in the development of colon cancer is the formation of aberrant foci of crypts. In this study, the number of the aberrant crypts reduced in the GL group revealing the therapeutic role of GL in colorectal cancer (Lu *et al.,* 2001). GL also reveal a protective effect against the formation of aberrant cyst when used as combination therapy with anti-cancer drug 5-FU. In another manuscript by Watanabe and group, rats were given azoxymethane (carcinogenic compound) subcutaneously once a week for a period of three weeks and then 5-FU (anti-cancer drug) was given intraperitoneally three times in a five-day interval. A group of mice received 5-FU in combination with GL, and it was observed that though 5-FU decreased the formation of aberrant cyst, more reduction was observed in the group with combination of 5-FU and GL, in the study, intestinal injury was caused by 5-FU and was later corrected by GL (Watanabe *et al*., 2013).

Irinotecan and SN38

Irinotecan (CPT-11) plays the role of DNA topoisomerase I inhibitor that stops DNA replication and obstructs RNA synthesis (Font *et al.,* 2002). CPT-11 has interesting antitumor properties against metastatic CRC (mCRC). Irinotecan can be used alone as a conventional treatment against CRC but studies have revealed that it has better anti-tumor effect when combined with 5-fluorouracil (5-FU) for mCRC treatment (Rougier *et al.,* 1997; Douillard *et al.,* 2000). Another alkaloid is SN38, it is an antineoplastic drug. It is an irinotecan analog. Al-Kasspooles and group reported that it has an inhibitory effect against malignant cell growth (Al-Kasspooles *et al.,* 2013). SN38 helps in inhibiting vascular endothelial growth factor (VEGF) and also aids the inhibition glioma cells' angiogenic activity. Studies have shown that despite the antitumor effect of CPT-11 and SN28, both have been linked to toxicity such as neutropenia and diarrhea (Hamano *et al.,* 2019; Iihara *et al.,* 2019).

Curcumin

Curcumin is well-known for its chemopreventive properties. Tong and colleagues revealed that curcumin has an anti-inflammatory and anti-tumoral activity (Tong *et al.,* 2016). Johnson and Mukhtar reported that in vitro studies of tumor cells in breast, liver and colon revealed that curcumin has antitumor effects (Johnson and Mukhtar, 2007). Camacho-Barquero and group reported that curcumin exhibits inflammatory activity by limiting the production of TNF-α and IL-6 (Camacho-Barquero *et al.,* 2007). In addition, curcumin might induce pro-apoptotic proteins' synthesis (such as Bax, Bak, Noxa) and impede anti-apoptotic proteins (such as Bcl-2, Bcl-xL) (Chen *et al.,* 2011). It also helps to stop metastases development by reducing VEGF and matrix metalloproteases (Durko and Malecka-Panas, 2014). Curcumin improves the effectiveness of conventional chemotherapy. Patel and group revealed that curcumin improves the effects of 5-fluorouracil (5-FU) and oxaliplatin in balancing growth inhibition of colon cancer cells by

regulating EGFR and IGF-1R (Patel *et al.,* 2008). Another study also revealed that the use of combination therapy that includes curcumin and bevacizumab helps in the inhibition of tumor growth (Yue *et al.,* 2016). Finally, Curcumin when used in association with FOLFOX chemotherapy, inhibits cancer cells and prevents colorectal and liver metastases (James *et al.,* 2015).

Resveratrol

Resveratrol is normally synthesized by plants as a result of pathogens attack by bacteria or fungi. It usually occurs in many plants such as peanuts, grapes, blueberries, and raspberries. Previous studies revealed that resveratrol plays a role in organism lifecycle regulation by acting as silent information regulation 2 homolog 1 (SIRT1), and also downregulates cyclooxygenase inflammation mediator enzyme, it has inhibitory potential against different types of cancer, which include breast cancer, gastric cancer, hepatocellular carcinoma and leukemia (Puissant *et al.,* 2010; Bishayee *et al.,* 2010). Resveratrol can also be used in combination with other chemotherapy molecules like 5-FU, mitomycin, oxaliplatin, curcumin and other natural products. Fulda and Debatin reported that resveratrol stimulates HCT116 (tumor cell line) and p53-deficient HCT116 colorectal carcinoma cell line leading to apoptosis in both lines (Fulda and Debatin, 2004). The use of 5-FU in CRC patients causes cytotoxic oxidative stress, and when resveratrol is used in combination with 5-FU, it aids the stimulation of SW620 and HT-29 cell lines (Santandreu *et al.,* 2011), which helps in reducing the stress. Resveratrol is very effective when used with other chemotherapeutic agents at a dose of about 1g (Patel *et al.,* 2010).

Cannabinoids

Cannabinoids are obtained from the plant called cannabis (*Cannabis sativa*). This plant contains three bioactive components which include flavonoids, terpenoids and cannabinoids (Chakravarti *et al.,* 2014). Cannabinoids have a therapeutic potential for cancer and studies confirming this claim have been shown in experimental models of CRC, brain tumor, breast cancer, melanoma and prostate cancer (Velasco *et al.,* 2016). Studies in animal models have revealed that cannabinoids have antitumor effects *in vivo* and *in vitro* by different mechanisms such as inducing apoptosis in cancer cells, proliferation inhibition (Hermanson and Marnett, 2011; Pisanti *et al.,* 2013). The apoptosis induction by cannabinoids is achieved through the upregulation of stress related genes (ATF-4, TRB3), ROS accumulation, proapoptotic proteins (BAX, caspase 3/9) activation and cell cycle arrests (Borelli *et al.,* 2014). As reported by Velasco and colleagues, another mechanism of apoptosis induction is the ceramide enhanced production via the mitochondria pathway (Valesco *et al.,* 2005). In this pathway, proapoptotic proteins are released into the cytosol binding together with cytochrome c, Apaf-1 and procaspase 9 to form the apoptosome leading to morphological and biochemical changes observed in apoptosis (Elmore, 2007). Cannabinoids aids the inhibition of proliferation and tumor growth. Studies revealed that the treatment of CRC cell lines with Δ^9- tetrahydrocannabinol which is the most active component of cannabis leads to inhibition of RAS-MAPK and PI3k-AKT pathways through the activation of CB-1 receptor (Velasco *et al.,* 2005). The importance of cannabinoids in treating CRC includes the upregulation of estrogen receptors, pro-inflammatory markers reduction, antiangiogenic effects and mitotic catastrophe.

Flavonoids

Flavonoids are mostly present in plant stems, leaves, seed and flowers. They are abundant in fruits and vegetables products including red wine, tea, coffee and some medicinal herbs (Nimptsch *et al.,* 2016). Studies have shown that flavonoids have many beneficial effects in diseases like cancers, Alzheimer's diseases and atherosclerosis (Castaneda-Ovando *et al.,* 2009). Flavonoids possess antioxidants properties, reduce proliferation of cancer cells, inhibit angiogenesis and enhance apoptosis (Lambert *et al.,* 2005). Flavonoids have the potential to alter cellular enzymatic functions such as cyclo-oxygenase (COX), lipoxygenase and xanthine oxidase, thus having a protective role in CRC (Metodiewa *et al.,* 1997). Flavonoids are classified into many subtypes depending on their chemical structure; the subtypes include flavanonols, flavanols, neoflavanoids, isoflavones flavones, anthocyanins, flavanones and chalcones (Panche *et al.,* 2016). The therapeutic effect of each of the subtypes and their molecular mechanism in CRC are discussed below.

Flavones

Flavones are mostly found in plants usually as glucosides. Flavones have different subclasses. In relation to CRC, the most investigated among flavones are luteolin, apigenin and tangeritin. Rossi and colleagues performed a case control study; 1,953 cases of CRC in comparison with 4,154 patients having acute non-neoplastic diseases. They investigated the association between different subtypes of flavonoids consumption with CRC. In this study, it was reported that flavones intake leads to reduction in CRC risk with an odd ratio of 0.78 in the group receiving flavones (Rossi *et al.,* 2006). In animal models, Ashokkumar and Sudhandiran performed an experiment investigating the effects of luteolin in Balb/c mice after azoxymethane was used to induce colon cancer. Luteolin reduced the number of aberrant crypt foci (ACF), so diminishing the lipid peroxidation. Azoxymethane induces CRC by inhibiting antioxidant enzymes such as SOD (superoxide dismutase), GPx (glutathione peroxidase), CAT (catalase) and GR (glutathione reductase). However, luteolin enhances the antioxidants' enzymes activity (SOD, GPx, GR and CAT). In this study, it was reported that luteolin has chemopreventive properties against CRC (Ashokkumar and Sudhandiran, 2008). Leonardi and group also performed a study using rats. In the study, Azoxymethane (AOM) was used to induce CRC in the rats. Results in the study revealed that 0.1% apigenin diet decreased the number ACF and increased apoptosis of CRC cells (Leonardi *et al.,* 2010).

Flavonols

Flavonols belong to a flavonoids' subgroup and are mostly found in fruits and vegetables, playing a role in defense against UV radiation and infection from pathogen. The most investigated among flavonols' subclasses are fisetin, myricetin, kaempferol, and quercetin. Other sources of flavonols are tea, onion, tomato, apple, lettuce and grape. In a clinical study by Farsad-Naeimi and colleagues, 37 CRC patients that were undergoing chemotherapy were registered in the study. It was reported that fisetin (100 mg) ameliorates the inflammatory condition in CRC patients, which underlines its antitumor properties (Farsad-Naeimi *et al.,* 2018). An *in vitro* study by Hosokawa and group revealed that quercetin reduced the growth of COLO320 DM cells (colon cancer cell line) by halting cell in G_1/S boundary and influence the synthesis of cell-cycle related 17-kDa proteins (Hosokawa *et al.,* 1990). In a similar study, Ranelletti and colleagues revealed that quercetin reduces p21-ras K- H-, and N-ras proteins CRC cell lines

and colorectal tumors (Ranelletti *et al.,* 2000). Raja et al. (2017) also performed a study to investigate the cytotoxic activity of quercetin on colonic cancer cells. It was reported in this study that quercetin partially inhibits COX-2 enzyme which in turn results in ROS accumulation and also induced cancer cells' activity (H-29, HCT15) via caspase-3 activation. Quercetin can also be used in combination with other chemotherapy. An observational study by Cruz-Correa and group revealed that combined therapy, that includes quercetin and curcumin, could decrease adenomatous polyps number and size in patients with familial adenomatous polyposis (Cruz-Correa *et al.,* 2006). Studies have also shown that quercetin, when used with aspirin or NSAIDs, reduced colon cancer risk (Simons *et al.,* 2009; Kyle *et al.,* 2010).

Flavanones

Flavanones are mostly found in citrus fruits. Reports have revealed that flavanones have anti-inflammatory, anticarcinogenic, antihypertensive and antioxidants properties (Tripoli *et al.,* 2007). Investigated subclasses of flavanones include hesperetin, naringenin, rutinosides and neohesperidosides. *In vivo* and *in vitro* studies have shown the inhibition of low-density lipoprotein oxidation and (HMG)-COA reductase after treatment with hesperetin (Bok *et al.,* 1999). In a similar study, Aranganatha and colleagues performed an experiment investigating the effect of hesperetin on male colon cancer-induced Wistar rats (DMH). It was found that hesperetin decreased the number of ACF formed and also improved tissue lipid peroxidation. It was also revealed that hesperetin regulates xenobiotic-metabolizing (Aranganathan *et al.,* 2009a; 2009b). In another study, it was reported that hesperetin reduces cell proliferation, inhibits angiogenesis and reduces COX-2 mRNA expression, which in turn results in apoptosis in male Wistar rats (Nalini *et al.,* 2012). In addition, another study revealed that naringenin reduces the growth of colon cancer cells in rats (Kuo, 1996). In fact, it was demonstrated that a nanocarrier (naringerin encapsulated soluthin-maltodextrin-based nanocarrier) improves the chemotherapeutic efficacy of naringenin against CRC (Chaurasia *et al.,* 2017).

Flavanols

Flavanols are mostly found in plants. The main subclass associated with CRC is the flavan-3-ols, and it is mainly found in tea (Cassidy *et al.,* 2010). Cocoa is also rich in flavanols. Flavanols have a positive impact on health; they are effective antioxidant possessing anticarcinogenic properties. They have a therapeutic effect against viruses and microbes and also protect from cardiovascular diseases. They have also shown therapeutic effects on CRC. (Aron and Kennedy, 2008). In a study where 34,651 postmenopausal women were registered, and followed-up from 1986 to 1998 including 635 colon cancer and 132 rectal cancer cases, it was revealed that the consumption of catechin (flavan-3-ol) reduced the incidence rate of rectal cancer (odd ratio, 0.55), but had no effect on colon cancer (odd ratio, 1.10) (Arts *et al.,* 2002). Randomized clinical trial studies revealed that daily consumption of 0.9-1.5g green tea for a period of 12 months reduces the colorectal adenoma risk (Shimizu *et al.,* 2008; Shin *et al.,* 2018). Previous studies have also revealed the anticarcinogenic effects of cocoa. Cocoa alters many carcinogenic pathways by inhibiting proliferation and inducing apoptosis in animal models (Martin *et al.,* 2013). An in vivo study also revealed the inhibition of colon cancer by cocoa-rich diet (12%). Wistar rats were induced with AOM and coca-rich diet prevented oxidative stress and inhibited cell proliferation through apoptosis. The diet also reduced NF-κB levels and pro-inflammatory enzymes (COX-2) in the colon (Rodríguez-Ramiro *et al.,* 2013). Asano and colleagues reported that epigallocatechin gallate (EPCG, type of catechin) also

possesses preventive properties against cancer (Asano *et al.,* 1996). Results from a study revealed that treating mice with EGCG significantly reduced cell growth (58%) and proliferation (27%) of xenocrafts of colon cancer, when the experimental group was compared with the control group (Jung *et al.,* 2001). Chen and group also suggested that EGCG suppresses Wnt/β-catenin pathway and angiogenesis (Chen *et al.,* 2017). Combination therapy of flavanols, in a study that included 36 patients with resected colon cancer and 51 patients after polypectomy, it was revealed that the combination of flavonoid mixture including daily intake of 20 mg apigenin and 20 mg EGCG reduced the neoplasia recurrence rate in resected colon treatment patients (47% in control, 7% in treated patients) (Hoensch *et al.,* 2008).

Anthocyanidins

Anthocyanidins are plants pigment. They are naturally found in grapes such as red and merlot grapes and berries such as blackberries, blueberries, strawberries, cranberries and raspberries. Anthocyanidins are structurally stable and have anti-inflammatory, antiviral and anti-cancer activities. The most investigated anthocyanidins include cyanidin, peonidin, malvidin and delphinidin. In a clinical study, a total of 1,953 patients (1,225 colon cancer; 728 rectal cancers) were followed-up for four years after dietary intervention of different subclass of flavonoids. It was reported that a significant reduction in the risk of CRC was observed in three subclasses of flavonoids (flavons, flavonols and anthocyanins) (Rossi *et al.,* 2006). In a study by Cooke et al. (2006), a group of ApcMin mouse models of intestinal carcinogenesis was supplemented with a mixture of cyanidin-3-glucoside and anthocyanin berries extract which comprises 15 components such as glucose, arabinose, galactose, cyanidin, peonidin, malvidin and delphinidin (mirtoselect). Another group of ApcMin mice were given only cyaniding-3-glucoside. It was reported that both mirtoselect and cyanin-3-glucoside improve the small intestine functions, but anthocyanidine appears to be more efficient than the cyanin-3-glucoside. Acai (*Euterpe oleracea*) which is a good source of anthocyanin, prevents colon cancer. Studies have revealed that 2.5% and 5% acai powder inhibits CRC development and induces apoptosis in DMH and AOM-induced CRC in animal models (Fragoso *et al.,* 2013; Romualdo *et al.,* 2015).

Terpenes

Terpenes are natural products that showed potential in preventing cancer. They are constituents of essential oils and mostly found in tea, citrus fruits and cannabis. *In vivo* and *in vitro* studies have revealed the antiproliferative role that terpenoids play in different type of cancers, including CRC (Huang *et al.,* 2012). Terpenoids are oxidized terpenes and are classified as mono, di, oligo and polyterpenes. The therapeutic effects of the different classes of terpenoids are discussed below.

Monoterpenes

Monoterpenes are mostly found in citrus fruits, lemon grass, ginger, aromatic herb oils, nutmeg, oregano and citronella oil. Mostly investigated monoterpenes include d-limonene, carvacrol, d-carvone and geraniol. D-limonene chemotherapeutic effect against CRC is linked to apoptosis induction and the regulation of polyamine metabolism. Jia et al. (2013) revealed that d-limonene induces apoptosis in LS174T colon cancer cells by increasing Bax/Bcl2 ratio, and also upregulating caspase-3, caspase-9 and cytochrome-c. Kawamori and colleagues performed an in vivo study to investigate the effect of d-limonene on F344

rats after inducing the rats with AOM. D-limonene was added to the drinking water. It was observed that d-limonene reduces the number of aberrant crypt foci (ACF) and also regulates the activity of ornithine decarboxylase (ODC), which suggests the chemopreventive nature of d-limonene. Likewise, previous studies also reported the chemopreventive effects of carvacrol against colon cancer. In fact, it was revealed that carvacrol has the potential to enhance endogenous antioxidants (SOD, CAT and GSH), ACF reduction and oxidative stress attenuation (Arigesevan and Sudhandiran, 2015; Sivaranjani *et al.,* 2016). D-carvone potential to regulate oxidative stress revealed its uniqueness in CRC therapy. In an in vivo study by Vinothkumar and group, CRC was induced in rats via DMH and d-carvone supplement effectively inhibited the DMH effect to induce pre-neoplastic colon injury (Vinothkumar *et al.,* 2013). Geraniol has also been shown to possess an anti-proliferative effect against CRC cell lines. The effect of geraniol with dose range between 100 and 500 μM was assessed in Caco2 cells and it was revealed that the concentration of 400 μM inhibited 70% cell growth. Reduction in the activity of ornithine decarboxylase (ODC) in addition to the increase in the activity of S-Adenosylmethionine Decarboxylase (AdoMetDC) in colon cancer cells suggests its potential to induce intracellular polyamine degradation pathway which in turn induced apoptosis (Carnesecchi *et al.,* 2001). As regards combination therapy, Carnesecchi and colleagues furthered the study by investigating the anti-proliferative effect of the mixture of geraniol (400 μM) and 5-FU. It was revealed that the mixture of both (400 μM geraniol and 5-FU) exerts an anti-proliferative effect that doubles the effect obtained when 5-FU was used alone. In facts, it was revealed that geraniol improved the transport of 5-FU and also inhibited intestinal hydrolases expression and therefore halting the differentiation of cancer cells (Carnesecchi *et al.,* 2002).

Sesquiterpenes

They are mostly found in higher plants, marine organisms and fungi. Most investigated sesquiterpenes include the isobutyroplenolin, arnicolide D, costunolide and zerumbone. Huang et al. (2014) reported that isobutyroplenolin and arnicolide D inhibit cell proliferation and cause apoptosis in HT-29 (colon cancer cells) via NF-kB inhibition and increase in the production of ROS. In another study, Tanaka et al. (1995) reported that costunolide reduced the number of ACF, as well as the activity of ODC in AOM-induced CRC in rats. It was also reported that supplement of zerumbone to AOM+DSS administered in rats lowers NF-kB and heme oxygenase (HO)-1 expression, and this can be linked to its anti-proliferative properties (Kim *et al.,* 2009).

Diterpenes

Diterpenes can be found in plants, bacteria, fungi and other animals. Investigated diterpenes include andrographolide, carnosol, pseudolaric acid, triptolide and kahweol. Studies have revealed that andrographolide has a cytotoxic effect on different cell lines which include melanoma, leukaemia, breast cancer and colon cancer (Rajagopal *et al.,* 2003; Nanduri *et al.,* 2004). Shi and colleagues reported that colon cancer cell line with androgapholide influence p53, p16 and p21 expression which in turn leads to the delay in G1-S phase (Shi *et al.,* 2008). A study revealed that daily supplementation of andrographolide at two different doses (250mg/kg, 500mg/kg) reduced ACF and also the cell proliferation marker PCNA in AOM-rats' colon (Al-Henhena *et al.,* 2014). Pseudolaric acid B is a type of diterpene that is found at the bark of the tree *Pseudolarix kaempferi Gordon* and it is mostly used in anticancer research because of its cytotoxic effects against different type of cancer cells (Pan *et al.,* 1990). Ko and colleagues revealed

that pseudolaric acid B causes cytotoxicity in HT29 cells through DNA fragmentation, G2/M phase arrest, and cyclins modulation (Ko *et al.,* 2007). Carnosol causes mitochondrial mediated apoptosis via the generation of ROS. It also increases the expression of p53. Moran and group studied the effect of carnosol on adenoma formation in a C57BL/6J/Min+ (Min/+) mouse model, which has a mutation in APC (adenomatus polyposis gene) gene. It was reported that carnosol supplementation reduced tumor multiplicity by 44% (Moran *et al.,* 2005). Triptolide is a diterpenoid that is found in *Tripterygium wilfordii* (a Chinese medicinal herb). It was revealed that SW114 colon cancer cells treated with triptolide decrease NO and PGE2 production and down-regulation of iNOS, and COX2 (Tong *et al.,* 2007). In combination therapy, the use of triptolide with oxaliplatin has antitumor effects on colon cancer. In a specific study, a nude mouse model affected with tumor was treated with triptolide and oxaliplatin. Results reported a significant decrease in the tumor size compared to those treated with either triptolide or oxaliplatin (Liu *et al.,* 2014).

Tetraterpenoids

Tetraterpenoids are generally found in fruits and vegetables, especially in tomatoes and carrots. Most investigated tetraterpenoids include lycopene and β-carotene. Scolastici et al. (2007) reported that tetraterpenoids protect vital biomolecules (DNA, enzymes, protein), which in turn prevent cancer initiation. The treatment of HT-29 and HCT-16 cells with lycopene is associated with a decrease in cell growth. In a study conducted by Dias and colleagues, it was reported that lycopene supplements decrease the ACF, PCNA and p53 and therefore induce apoptosis in rats exposed to DMH (Dias *et al.,* 2010). In a similar study by Tang et al (2008), it was reported that lycopene causes cytotoxic reaction on HT-29 cells by down-regulating Akt signaling pathway and thus induces apoptosis. Other studies have shown that β-carotene supplements inhibit tumor progression in AOM-induced rats by reducing aberrant crypt formation (Choi *et al.,* 2006; William *et al.,* 2009).

CONCLUSION

This chapter summarizes previously published works on natural products found in plants and other sources, and their chemopreventive properties and anti-tumor effects against CRC. Natural products have antioxidant (chemoprotective) and prooxidant (pro-apoptotic) properties, which confirms its antiproliferative actions. Conventional chemotherapy poses many burdens on patient's health, but the use of natural products in combination has been shown to reduce the toxic issue by conventional chemotherapeutic agents, such as 5-FU or oxaliplatin. Combining natural products with the conventional chemotherapy seems to be a promising approach in reducing the risk of CRC because combined therapy targets multiple signaling pathways. Also, there is dearth of information about clinical trials involving the use of natural products against CRC. Therefore, more studies are needed.

Table 1. Summary of natural products and their effects on CRC

Compounds		Mode of Action/Effects	References
Ganoderma lucidum		Reduction in oxidative DNA damage and inhibition of the formation of reactive oxygen species (ROS).	Sliva, 2003; Chang *et al.,* 2014.
Irinotecan		DNA replication and obstructs RNA synthesis	Font *et al.,* 2002.
SN 38		Inhibiting vascular endothelial growth factor (VEGF) and angiogenic activity of glioma cells.	Al-Kasspooles *et al.,* 2013.
Curcumin		Reduce the production of TNF-α and IL-6. It also induces pro-apoptotic proteins (Bax, Bak, Noxa) and impede anti-apoptotic proteins (Bcl-2, Bcl-xL)	Camacho-Barquero *et al.,* 2007; Chen *et al.,* 2011.
Resveratrol		Downregulates cyclooxygenase inflammation mediator enzyme	Puissant *et al.,* 2010
Cannabinoids		apoptosis in cancer cells, proliferation regulation and angiogenesis	Hermanson and Marnett, 2011
Flavonoids			
Flavones	Luteolin	Reduction in the number of aberrant crypt foci (ACF) and lipid peroxidation	Ashokkumar and Sudhandiran, 2008
	Apigenin	Decrease in the number ACF and increase apoptosis of CRC cells	Leonardi *et al.,* 2010
Flavonols	Fisetin	Induces apoptosis	Farsad-Naeimi *et al.,* 2018
	Quercetin	Reduces the growth of colon cancer cell by halting cell in G_1/S boundary, reduces p21-ras K- H-, and N-ras proteins CRC cell lines and colorectal tumors.	Hosokawa *et al.,* 1990; Ranelletti *et al.,* 2000
Flavanones	Hesperetin	Inhibition of low-density lipoprotein oxidation and (HMG)-COA reductase, decreased the number of ACF formed and also improved tissue lipid peroxidation.	Bok *et al.,* 1999; Aranganathan *et al.,* 2009a; 2009b
	Naringenin	Inhibits cell proliferation	Kuo, 1996.
Flavanols	Catechin	Inhibits cell proliferation and induces apoptosis	Martin *et al.,* 2013
	Epigallocatechin gallate	Suppresses Wnt/β-catenin pathway and angiogenesis	Chen *et al.,* 2017
Anthocyanidins	Cyanidin-3-glucoside (C3G)	Reduces adenoma number	Cooke et al., 2006
	Açaí powder/pulp (AP)`	Reduction in number of invasive tumor and multiplicity, reduction in the number of ACF	Fragoso *et al.,* 2013
Isoflavones	Soy Isoflavones	Reduction in ACF and expression of COX-2	Min *et al.,* 2010
	Genistein	Reduced tumor number, enhanced enterocyte migration rate, and adherens junction proteins (E-cadherin and b-catenin), increased the expression of ERb	Javid *et al.,* 2005
	Calycosin	Reduced tumor growth via ERβ-mediated regulation of the IGF-1R, PI3K/Akt signaling pathways and of miR-95 expression	Zhao *et al.,* 2016
Terpenes			
Monoterpenes	D-limonene	Increases caspase-3, -9 and Bax/Bcl2 and also reduction in ACF, AgNOR count.	Kawamori *et al.,* 1996
	Perillyl alcohol	Down-regulation of ras and p34, cyclin D1 and E, Cdk4, Cdk2 which in turn leads to growth arrest in the G1 phase.	Bardon *et al.,* 2002
	Carvacrol	Upregulation of SOD, catalase, GSH and downregulation of NO, iNOS, IL-1β. Reduction of ACF	Arigesavan and Sudhandiran, 2015
	D-Carvone	Regulate oxidative stress and reduces ACF	Vinothkumar *et al.,* 2013
	Geraniol	Induce intracellular polyamine degradation pathway which in turn induced apoptosis	Carnesecchi *et al.,* 2001
Sesquiterpenes	Isobutyroplenolin and Arnicolide	Induction of apoptosis and inhibition of cell proliferation	Huang *et al.,* 2014
	Costunolide	Reduction in the number of ACF and in the activity of ODC	Tanaka *et al.,* 1995
	Zerumbone	Lowering NF-kB and heme oxygenase (HO)-1 expression which in turn leads to inhibition of cell proliferation	(Kim *et al.,* 2009
Diterpenes	Andrographolide	Influences p53, p16 and p21 expression which in turn leads to delay in G1-S phase	Shi *et al.,* 2008
	Pseudolaric acid	Causes DNA fragmentation, G2/M phase arrest and cyclins modulation	Ko *et al.,* 2007
	Carnosol	Causes mitochondrial mediated apoptosis via the generation of ROS. Increases the expression of p53.	Moran *et al.,* 2005
	Triptolide	Decreases NO and PGE2 production and down-regulation of iNOS and COX2	Tong *et al.,* 2007

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Chapter 5
Natural Products for Treating Colorectal Cancer:
Topical Update on Natural Candidates Against Colorectal Cancer

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ABSTRACT

Colorectal cancer (CRC) is one of the causes of cancer-related mortalities across the globe. Epidemiological studies reveal the risk factors for CRC are genetic and environmental factors. The current therapeutic methods for CRC are associated with side effects and drug resistance. Gut microbiome therapy is one of the recent approaches for the prevention of CRC, reducing its progression and improving the effectiveness of colorectal cancer treatment by modulating the gut microbiome. The use of phytoconstituents is another approach. These compounds increase the gene expression of the cell cycle inhibitors and protein levels. This chapter summarizes the role of the gut microbiome and modification of the gut microbiota to improve treatment efficacy and minimize adverse effects of CRC therapies. Natural candidates like gut microbes and plant-derived bioactive components demonstrate their efficacy in appropriate in vivo models and clinical studies, which may lead to the discovery of alternative therapies for colorectal cancer.

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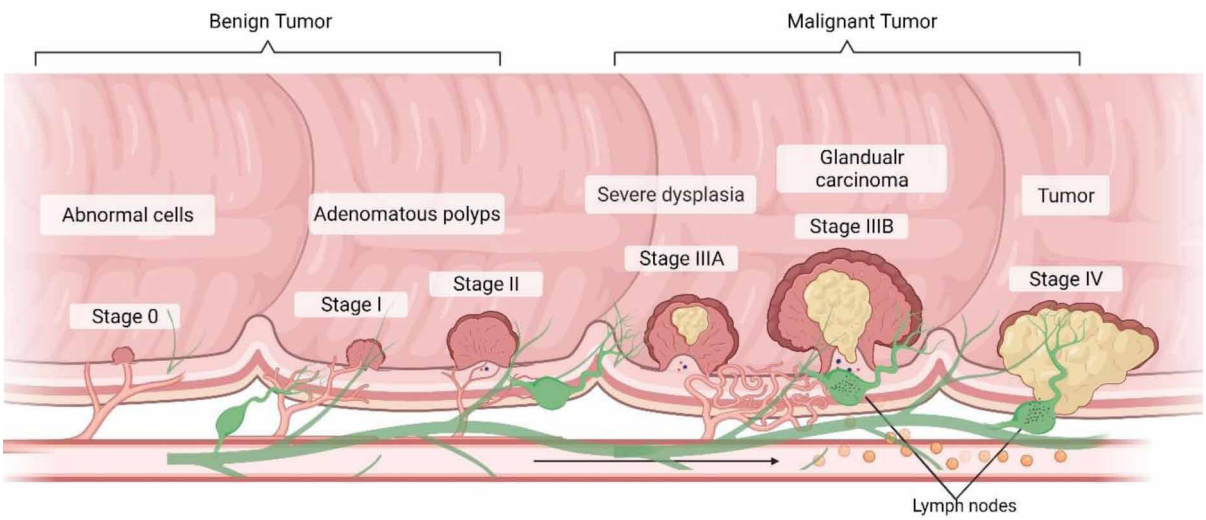
Figure 1. Stages of Colorectal cancer (Courtesy by biorender.com)



INTRODUCTION

Carcinogenesis is a multistage process consisting of initiation, promotion, and progression phases involving sequential generations of cells that exhibit continuous disturbance of cellular and molecular signal cascades (Rajamanickam & Agarwal, 2008). Cancer is a disease in which some cells of the body proliferate uncontrollably, multiplies incessantly, form tumor, spread to other regions of the body, and encourages growth of blood vessels to obtain nutrients. A tumor can be of two types, malignant and benign. Malignant tumors are more dangerous that can easily metastasize by entering into the blood circulation or lymphatic system. Whereas, a benign tumor can grow but restricted to one area and will not spread (Pandurangan et al., 2016). These changes are caused by both genetic and environmental factors and usually take years to develop.

There are more than 120 different types of cancers. Among them colorectal cancer (CRC) is one of the most common types of cancers in humans and is closely linked to the global cancer-related mortalities worldwide. Figure 1 shows the stages of colorectal cancer. Signs and symptoms of the disease may include blood in the stools, changes in bowl movement, weight loss and fatigue.

Prevention of CRC usually depends on screening methods to diagnose adenomatous polyps which are precursor lesions to colon cancer. The present treatment for colon cancer is generally based on using cytotoxic drugs, radiotherapy, chemotherapy, and surgery. Apart from these treatments, natural products are also used for the treatment and control of colon cancer progression (Aiello et al., 2019).

Intestinal dysbiosis plays an important role in CRC development. The gut microbiota contain a large population of microorganisms that interact directly with host intestinal cells and can affect immunity and metabolic activities in the gastrointestinal tract (Guinane & Cotter, 2013). Significant changes in composition and quantity of specific bacteria can be detected in patients with CRC and might use as biomarkers for disease screening, prognosis and to predict its response to treatment (Villéger et al., 2018). Different approaches including prebiotics, probiotics, postbiotics, antibiotics, and fecal microbiota transplantation (FMT) have been used to implement gut microbiome (Kaźmierczak-Siedlecka et

al., 2021). These approaches show promising results, arbitrarily by correcting microbiome composition, regulate innate immune system, preventing pathogen colonization and exerting selective cytotoxicity against tumor cells (Fong et al., 2020).

Throughout history, natural products or herbal drugs have played important role in the treatment of human ailments. The crucial role played by natural products from medicinal plants in the discovery and development of novel anti-colon cancer agents (Benarba & Pandiella, 2018). Historically, plants have been rich sources of natural product drug discovery, and in the anticancer area. Plant-derived product, such as vincristine, etoposide, paclitaxel, docetaxel, topotecan, and irinotecan, are among the most effective cancer chemotherapeutics currently available (Cragg & Pezzuto, 2016).

The potential of natural compounds such as flavonoids, anthocyanins, alkaloids, carotenoids, and terpenoids for cancer prevention has been widely investigated (Câmara et al., 2021). So many shreds of evidence supporting that moderate consumption of fruits and vegetables are correlated with decreased risk of CRC (Liang & Binns, 2009). Some natural compounds have the ability to modulate signalling pathways as well as to regulate the expression of genes involved in cell cycle regulation, differentiation, and apoptosis. As wellbeing useful in the prevention, some of these molecules could be also helpful for the treatment of CRC (Redondo-blanco, 2017). There is a resurgence of interest in natural products such as medicinal plants and their extracts as an alternative solution to curing CRC (Graziani et al., 2018).

The study of nutrition's influence in the cancer process spans a wide range of topics. As research progresses, it is increasingly obvious that nutrition plays a significant role in cancer. Colorectal cancer outcomes may be influenced by nutrients. (Donaldson, 2004). (Du & Fang, 2015). Selenium, folic acid, vitamin B-12, vitamin D, and Vitamin C (ascorbic acid) have all been suggested as potential agents for preventing colorectal cancer in a cancer prevention diet. Some studies, however, concluded that these nutrients had no effect on the incidence of colorectal cancer. The supplemental nutrient dose, the time required to notice the effects, and confounding circumstances throughout the trial could all have an impact on the role of nutrients in colorectal cancer prevention (Du & Fang, 2015). At the higher quintiles, vitamin B6 and vitamin B12 consumption protects against colon cancer. At all levels of consumption, dietary vitamins E and C are significantly protective against colon cancer, with a dose-response impact. Some dietary micronutrients with antioxidant qualities (vitamins C and E) and those involved in DNA methylation, synthesis, and repair (folate, vitamins B6 and B12) may have a role in lowering colorectal cancer risk (Kune & Watson, 2006). In various genetic models of bowel cancer, vitamin D and its equivalents diminish the growth of colon cancer xenografts and suppress carcinogenesis. In agreement, treatment with vitamin D3 and calcium has been demonstrated to inhibit dietary initiation of colon cancer in mice, a model of sporadic colon cancer (Muzny et al., 2012). Vitamin D suppresses Wnt signalling. 1,25D3 increases Vitamin D receptor (VDR)/β-catenin interaction in tumour cells, inhibiting β-catenin nuclear translocation. (Klampfer, 2014).

The current therapies available are not sufficiently effective and their efficacy is limited by the side effects of the drugs and/or the development of resistance. Therefore gut microbiome therapy and use of plant natural products have received great attention for colon cancer prevention owing to their various health benefits, noticeable lack of toxicity and side effects.

COLORECTAL CANCER (CRC)

Aetiology

According to the data from GLOBOCAN in 2012, there were 1.6 million new cases of CRC and 694,000 people that die from CRC every year (Huang et al., 2019). Recent data of GLOBOCAN 2020 estimates, 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred worldwide in 2020, with an estimated 10% diagnosed as colorectal cancer and nearly 9.4% of cancer deaths are due to CRC. World Health Organization (WHO) in 2019 estimated cancer is the first or second leading cause of death before the age of 70 years. In 2020, out of 36 different cancers, 732,210 (3.8%) numbers of new cases and 339,022 (3.4%) deaths are due to CRC. CRC is the third commonest neoplasm in both men and women (Sung et al., 2021). CRC is increasingly being diagnosed by colonoscopy nowadays, both at an early stage and advanced stage. Colorectal cancer (CRC) is one of the most common cancers. CRC is now ranked third in occurrence and second in mortality rate among all other cancers globally. CRC, which is also known as bowel cancer, colon cancer or rectal cancer is the development of cancer from the colon. The progression of colorectal cancer is caused by a multiple factors, such as age, diet, obesity, smoking, family history, gender, region, and personal history are the major risk factors to cause the CRC (Huang et al., 2019). Signs and symptoms may include blood in the stool, a change in bowel movement, weight loss, and fatigue. Colon or rectum is located at the lower end of the digestive tract. Early-stage colon cancer starts as non-cancerous polyps. It does not show any symptoms then it can be detected by screening. This is a very common type of preventable cancer. Generally, in CRC 71% are in the colon and 29% are in the rectum. From 2008 to 2014, the incidence of CRC decreased slightly in men (2.2% per year) but remained stable in women. The mortality rate of CRC was decreased up to 1.8% per year among men and 1.4% per year among women from 1999 to 2015. Nearly 70% of CRC occurs in the average risk individuals, 25% of the patients are with a family history of CRC and about 10% are with hereditary colorectal cancer syndromes (Ahmed, 2020).

Risk Factors for CRC

Both genetic and environmental factors play an important part in the aetiology of colorectal cancer. In most western populations, the average lifetime risk factors for colorectal cancer range is 3-5% (Kuipers et al., 2015). Most of the colon cancers about 95% are considered sporadic, which means the genetic changes develop by chance after a person is born, and also there is no risk of passing these genetic changes onto one's children. However, some of the following factors are responsible for the risk to get colorectal cancer in persons those include, age, race, gender, family history of colorectal cancer, rare inherited conditions, physical inactivity and obesity, food/diet and smoking and alcohol consumption.

Age, Race, and Gender

Age factor is one of the risks of colorectal cancer in which it increases as people get older. Majority of colorectal cancer occur in people older than 50 years. The CRC in people of age group 50 to 79 years and 40 -49 years group are more frequent to get the colorectal cancer of stage III and stage IV (Steele et al., 2014). It has been suggested that the average age at the time of diagnosis for men is 68, for women is 72.

Food/Diet

Diet has been a popular subject for colorectal cancer research. Dietary fibers are open for future prospects. Several authors have asserted a protective role for calcium, vitamin D, and other dietary factors such as foliate, vitamin B6, magnesium, garlic, omega-3-fatty acids. On the other hand, frequent consumption of red meat and fat has been associated with increased risk for the development of colon cancer (Hadjipetrou et al., 2017).

Obesity

Obesity is one of the relative risk for colorectal cancer, depending on the country. Colorectal cancer risk is more in male with obese as compared to obese female (Bardou et al., 2013). Body mass index (BMI) is important for healthy person and diseased person and for CRC, each $2kg/m^2$ increase weight accounted for a 7% of chance of getting high-risk colorectal cancer (Tandon et al., 2015)

Family History of Colorectal Cancer

Most colorectal cancers are found in people with a family history of colorectal cancer as many as 1 in 3 people who develop colorectal cancer have other family members who have had it, people, with a history of colon cancer in the first degree of relative (parent, sibling, or child) are at increased risk (Henrikson et al., 2015).

Smoking and Alcohol Consumption

Several shreds of evidence show that 12% of deaths are attributed to smoking, evidence also demonstrates an earlier average age of onset of colorectal cancer among men and also alcohol consumption is a factor in the onset of colorectal cancer at an younger age (Haggar & Boushey, 2009).

TYPES OF COLORECTAL CANCER AND MOLECULAR CHARACTERISTICS

Several types of CRC are known, the most common one is adenocarcinoma. Others include carcinoid tumors, gastrointestinal stromal tumors, and colorectal lymphoma. Hereditary colorectal cancers (several generations of a family have had colorectal cancer) include hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP).

The major cause for colorectal cancer is probably the genes that are affected by cancer-causing mutations, their normal functions, and their carcinogenic effects when mutated (Ahmed, 2020). Understanding of the molecular genetic processes occurring in cancer depends on the identification of both high and low-penetrance mutations (De'angelis et al., 2018). This facilitates the development of therapeutic drugs and preventive strategies. In addition to that, gene-gene and gene-environment interactions have a significant influence on susceptibility to colorectal cancer.

There is a definitive genetic etiology for approximately one-third of most of the familial cases of CRC (Hisamuddin & Yang, 2006). Formation of precursor lesions in the form of either adenoma or hamartoma is the characteristic of these genetic predispositions to CRC (Chapelle, 2004).

An adenoma is derived from cells of the colonic epithelium and hamartoma from cells of the stroma. However, both lesions pose an increased risk for CRC. The majority of the genes involved in hereditary CRC syndromes are tumor suppressor genes (TSGs), and mutations in these genes are transmitted in the germline. The primary cause for the two major types of familial predisposition to adenoma formation: FAP and HNPCC are the mutations in the adenomatous polyposis coli (APC) and mismatch repair (MMR) genes respectively. Familial predisposition to hamartoma formation is also called juvenile polyposis syndrome (JPS) and contains many sub-types. The following Table 1 has the summary of various hereditary colorectal cancer and polyposis syndromes with regard to the mechanisms of action of the respective TSGs responsible for the various hereditary colorectal cancer syndromes (Kinzler & Vogelstein, 1998).

Diagnostics of Colorectal Cancer

Most of the tumors are localized in the rectum (37%), and sigmoidal (31%), being less frequent in ascending colon (9%), cecum (8%), descending colon (5%), transverse colon (4%), hepatic angle (4%), and splenic angle (2%).

Endoscopy

For the diagnosis of colorectal cancer, colonoscopy is the best method of choice. Colonoscopy identification of advanced lesions is relatively straightforward, but early colorectal cancers might appear as very subtle mucosal lesions.

Imaging

CT colonography is used as a complementary imaging method for the diagnosis of polyposis and colorectal cancer. Imaging methods are mostly used for accurate locoregional (done by MRI) and distant staging.

Laboratory Methods of Diagnosis for CRC

In addition to obtaining a complete blood count, the elevated baseline carcino-embryonic antigen concentrations are determined at the time of diagnosis. An elevated baseline is associated with worse prognosis, and concentrations that do not normalise in the post-operative phase which might indicate as residual disease (Paulus, 2020).

Therapeutic Actions Toward Colorectal Cancer

Surgery

Stage 0 cancer can be treated by removing cancer cells by colonoscopy. For stage I, II and III cancer, it is necessary to perform surgery by using radical colectomy, the laparoscopic approach is to be considered a safe and traditional open approach for colorectal cancer. In patients with stage III colorectal cancer receive the complimentary chemotherapy after surgery for 6 to 8 months, in order to improve the symptoms and prolonged survival (Xu et al., 2020).

Table 1. Summary of various hereditary colorectal cancer and polyposis syndromes

Syndrome	Genes	Inheritance	Risk of CRC	Mechanism	Reference
Adenomatous polyposis syndrome					
Familial adenomatous polyposis (FAP)	APC	AD	1	Germline mutations in the APC gene.	(Kinzler et al., 1991) (Nishisho I et al, 1992) (Groden et al., 1991)
Attenuated FAP	APC	AD	>90%	Mutations in the APC transcript (extreme 5′ or 3′ terminus)	(Soravia et al., 1998)
The APC I1307K mutation	APC I1307K	AD	~ 10%	Transversion mutation (T to A) in nucleotide position 3920 of the APC coding region and consequent substitution of amino acid lysine (K) residue for an isoleucine (I) residue in 1307 position of the APC protein.	(Steven J. Laken, Gloria M. Petersen, 1997)
Hereditary nonpolyposis colorectal cancer or Lynch syndrome	hMLH1 hMSH2 hMSH6 hPMS1 hPMS2	AD	0.8	The absence of critical function of MMR genes leads to the accumulation of errors in repeated DNA sequences called microsatellites. HNPCC patients exhibit microsatellite instability (MSI). Mutations in the MMR genes leads to inactivation of downstream genes due to MSI. There are some of the target genes exhibiting cell proliferation regulation like type II receptor for transforming growth factor β (TGF-β RII), the receptor for insulin-like growth factor II (IGFIIR), and BAX that is involved in the control of apoptosis. Inactivation of these genes leads to a derangement in cell proliferation and subsequent tumor formation.	(Papadopoulos & Lindblom, 1997) (Markowitz et al., 1995) (Souza et al., 1996) (Rampino et al., 1997)
Muir-Torre	hMLH1 hMSH2	AD	0.8	Same as Lynch syndrome	(Irfan et al., 2006)
MYH-associated polyposis	MYH	AR	1	The MYH gene functions in base excision repair (BER) and bi-allelic mutations leads to the phenotype, now called MYH-associate polyposis (MAP).	(Sieber et al., 2003)
Hamartomatous (juvenile) polyposis syndrome					
Peutz-Jeghers syndrome (PJS)	LKB1/ STK11	AD	0.4	In more than half of the patients with PJS, germ-line mutations of the LKB1/STK11, a serine-threonine kinase gene are found.	(Hemminki et al., 1998) (D E Jenne, H Reimann, J Nezu, W Friedel, S Loff, R Jeschke, O Müller, W Back, 1998)
Juvenile polyposis coli	SMAD4 BMPRIA PTEN	AD	10%–40%	Mutation in the following three genes have been linked to JPS, the TGF-β signalling genes SMAD4 and BMPR1A, and PTEN, a tumor suppressor gene with phosphatase activity.	(Olschwang et al., 1998)
Cowden syndrome	PTEN	AD	No change	Mutations in PTEN	(Marsh et al., 1999)
Bannayan-Riley-Ruvalcaba syndrome	PTEN	AD	10%–40	Mutations in PTEN	(Marsh et al., 1999)
Others					
Turcot's syndrome (FAR variant)	APC hMLHI hMSH2	AD	1	Associated with MMR mutations.	(Soravia et al., 1998)
Hereditary mixed polyposis syndrome	Unknown	AD	0.3	Unknown	(Irfan et al., 2006)

AD=Autosomal dominant; AR=Autosomal recessive

Radiotherapy for Colorectal Cancer

A several historical trials have shown that the benefit of pre-operative radiotherapy while opposed to post-operative radiotherapy, which reduces the risk of local recurrence. The absolute risk reduction is achieved by preoperative radiotherapy that depends on the clinical stage and quality of surgery (Paulus, 2020).

Chemotherapy

Adjuvant chemotherapy for patients with stage II and stage III colon cancer shows benefit for patients after surgery (Varghese, 2015). The chemotherapeutic drugs such as 5-Fluorouracil (5-FU), Irinotecan, Oxaliplatin, Trifluridine and Tipiracil (Lonsurf) are used to treat the colorectal cancer (Goyle & Maraveyas, 2006).

Immunotherapy

It is a new mode of cancer treatment and has the most promising role in gastrointestinal malignancies. T-cell mediated immune suppression is one of the main hyper-progression and about 65% of patients with colorectal cancer get benefit from nivolumab (monoclonal antibodies) (Golshani & Zhang, 2020).

Ablation for Colorectal Cancer

Radiofrequency ablation induces coagulation necrosis of tumor tissue by generating heat and it is one of the effective methods with patients of about 1-5% complications. The interstitial brachytherapy, as well as locoregional therapies, plays prominent role in local tumor control, extensive cytoreduction with low morbidity and mortality (Seidensticker et al., 2018).

Side Effects of Cancer Treatment

Hair loss

Most common side effect in patients with cancer after chemotherapy treatment seen in 2-4 weeks of initial chemotherapy.

Mucositis

Opportunistic fungal infection can occur from mouth to anus usually after chemotherapy (5-FU, etc.)

Hand-foot syndrome (Chemotherapy-induced acral erythema)

There is reddening, swelling, numbness and desquamation on palms of the hands and soles of the feet occur after chemotherapy, it can develop during the treatment with capecitabine or 5-FU.

Neuropathy

Nerve damage is common side effects of oxaliplatin, and the symptoms include numbness, tangling and pain in hands and feet.

Diarrhoea

It is the most common side effect with many of chemotherapeutic drugs especially for irinotecan.

Other side effects include mouth sores, nausea and vomiting, nail changes, skin changes and allergic or sensitive reactions (American cancer society cancer.org).

NATURAL CANDIDATES

In this chapter two types of natural candidates for the CRC treatment and their mechanism of action are discussed. First one is the gut microbiome therapy that includes different microorganisms of the intestine, their harmful and beneficial effects, use of these microbes in the diagnosis and treatment of colorectal cancer. Second therapy being the plant secondary metabolites like terpenoids, alkaloids and flavonoids, are the natural candidates used for the CRC treatment which have tested for anti-cancer property, their structures and mechanisms are discussed.

Biotherapy for Colorectal Cancer on the Basis of the Gut Microbiome

Intestinal dysbiosis plays a vital role in the CRC development (Wieczorska & Stec, 2019). The gut microbiota contains a large population of microorganisms that interact directly with host intestinal cells and it can affect the immunity and metabolic activities in the gastrointestinal tract (Chen, 2018). This composition is influenced by maternal colonization, diet, environmental exposures, and antimicrobial therapies. Significant changes in composition and quantity of specific bacteria can be detected in patients with CRC and might use as biomarkers for disease screening, prognosis and to predict its response to treatment (Sekirov et al., 2010). The experimental evidence shows that, the gut microbiome of healthy individuals is remarkably different from that of patients with CRC suggests that the microbiota can serve as biomarkers for CRC detection. The stool samples from 30 healthy and CRC patients identified six different bacterial populations, or operational taxonomic units (OTUs) that were associated with CRCs. In addition, considering other risk factors such as age and body mass index (BMI), the use of these biomarkers considerably improved the ability to discriminate between healthy and cancer patients (Chen, 2018). Mainly the gut microbiota consists of strict anaerobes, which dominate the facultative anaerobes and aerobes. Human gut microbiota is dominated by Bacteroidetes and Firmicutes, while Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria and Cyanobacteria are less in number.

Number of bacterial species present in the human gut may vary widely from different studies, but generally, it has been accepted that it contains 500 to 1,000 species (Sekirov et al., 2010). Table 2 contains harmful bacterial species in CRC patients and the mechanism to elevate tumor progression and Table 3 has information about useful species of bacteria and their role in preventing CRC. Late CRC samples (stage III and stage IV) generally display higher richness levels than early CRC samples do (stage I and stage II).

Table 2. Harmful bacterial species in CRC patients and the mechanism to elevate tumor progression

Genus/Species	Animal model	Occurrence in colon CRC	Mechanism
Fusobacterium nucleatum Gram negative	APC(Min/+) mice	87.13%	Increases expression of pro-inflammatory cytokines. Increases tumor growth by triggering c-JUN/JNK and STAT3 signaling pathways (Sánchez-Alcoholado et al., 2020) (Ren et al., 2021)
Bacteroides fragilis Gram negative	Mice and human	58.3%	Toxin activates Wnt and NF-kB signalling pathway (C. Lin et al., 2019).
Escherichia coli Gram negative	Human	55.3%	Colibactin toxin causes DNA cross links and ds DNA breaks (Choudhry, 2021).
Helicobacter pylori Gram negative	Human	41%	Increases inflammatory cytokines (Ren et al., 2021).
Streptococcus gallolytics. Gram positive	Human-Rodent	20-40%	Expression of COX-2 Inflammatory, immune response (Torres-Maravilla et al., 2021).
Clostridium septicum Gram positive	Human- Rodent	40%	Increases TLR4-mediated inflammatory response in macrophages (Jahani-Sherafat et al., 2018).
Enterococcus faecalis Gram positive	Human- Rodent	50.8%	ROS production and DNA damage (Ren et al., 2021)
Camphylobacter jejuni Gram negative.	APC(Min/+) mice	41-60%	Genotoxin, induce dsDNA breaks (Ren et al., 2021).

Table 3. Beneficial species of bacteria and their role in preventing CRC

Bacterial Species	Animal model	Mechanism
Lactobacillus acidophilus, L. plantarum, L. casei, L. lactis, L. butyricum, L. salivarius, L. reuteri, L. bulgaricus. Gram positive	CT-26 Mouse and Human	Antitumor effect due to reduced expression of CXCR-4, decrease in the levels of TNF-α, IL-6, increase in the levels of superoxide and catalase. Increases serum levels of IFN-γ and IL-10 and the number of $CD4^+$ and $CD8^+$ cells (Fong et al., 2020) (Torres-Maravilla et al., 2021).
Lactobacillus rhamnosus Gram positive	Human	Decrease the expression of Th17 cells and secretion of IL-23 and IL-7 via inhibition of STAT3 and NF-kB signalling (Sánchez-Alcoholado et al., 2020).
Bifidobacterum infantis. B. breve, B. bifidum. Gram positive	Rodent- human	Interact with TLRs, able to activate intestinal dendritic cells, leading to the expression of Fox3+ regulatory T cells and IL-10 release (Torres-Maravilla et al., 2021). .
Clostridium butyricum Gram positive	Rodent/ human	Decrease in tumor size, decreased amounts of Th2 and Th17, inhibition of CD4+ and CD8+ T lymphocytes, decrease in NF-kB and IL-22 (C. Lin et al., 2019).
Megasphaera massiliensis Gram negative	Rodents	Increased levels of the SCFA pentanoate and butyrate, inhibition of histone deacetylases (HDACs), increase in effector cytokines in CD8+ T cells (Luu et al., 2021).

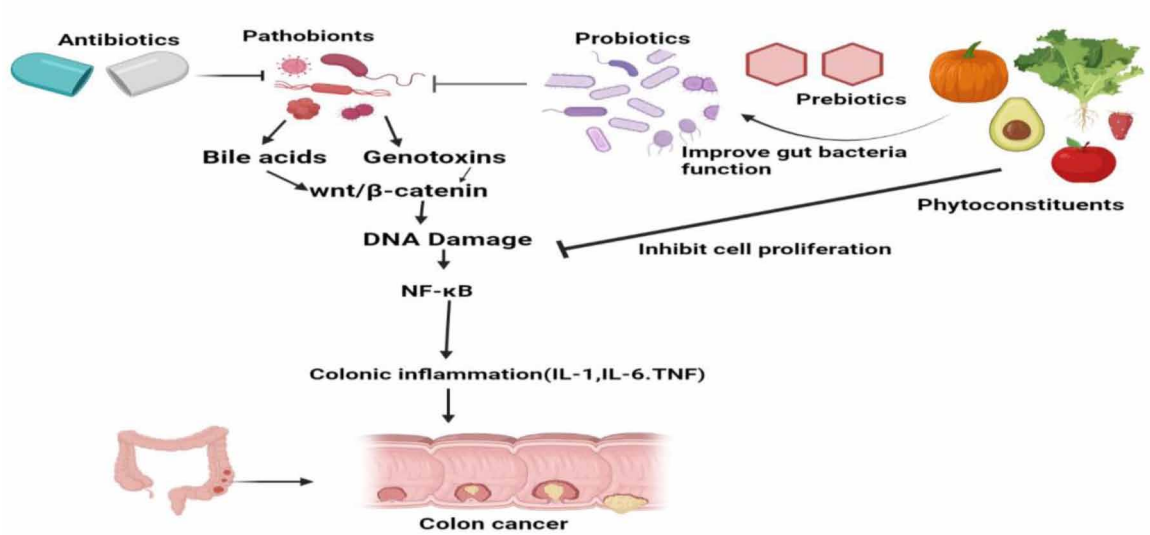
The gut microbiota produces various metabolites such as short-chain fatty acids (SCFAs), polyphenols, vitamins, tryptophan catabolites and polyamines that may harm or benefit the host (Sánchez-Alcoholado et al., 2020). The SCFAs pentanoate and butyrate elevate the anti-tumor activity of cytotoxic

T lymphocytes (CTLs) and chimeric antigen receptor (CAR) T cells through epigenetic and metabolic reprogramming. *In vitro* treatment of CTLs and CAR T cells with butyrate and pentanoate enhance the function of the mechanistic target of rapamycin (mTOR) as a central cellular metabolic sensor, and prevent the activity of class I histone deacetylase (Luu et al., 2021). Probiotics provide anti-inflammatory factors to enrich the immune-stimulating function, produce antioxidants, anti-cancer compounds, SCFs, and boost intestinal barrier function. Probiotics prevent carcinogenesis by decreasing cyclooxygenase-2 expression (Fong et al., 2020).

Different approaches including prebiotics, probiotics, postbiotics, antibiotics, and fecal microbiota transplantation (FMT) have been used to implement gut microbiome. These approaches show promising results, arbitrarily by correcting microbiome composition, regulate the innate immune system, preventing pathogen colonization and exerting selective cytotoxicity against tumor cells along with this, they are accompanied by risks and contentions that can probably introduce clinical complications (Fong et al., 2020). Also the combination of specific gut microbes and therapeutic agents, like immunotherapy, is synergistic in the natural treatment of CRC (Wieczorska & Stec, 2019).

There is hope for the prevention of colorectal cancer, reducing the risk of its progression, and improving the effectiveness of colorectal cancer treatment, by modulating the gut microbiome by changing the diet, minimizing broad-spectrum antibiotics, and using probiotics and prebiotics (Wieczorska & Stec, 2019). Modification of the gut microbiota is a promising approach to improve treatment efficacy and minimize adverse effects of CRC therapies (Figure 2). Future research strategies should look into the ideal ways to modulate the gut microbiota and to evaluate its short-term and long-term uses through clinical trials (Aarnoutse et al., 2017).

Figure 2. Pictorial Illustration of Impact of Phytochemicals and the Gut-microbiome on Colorectal cancer (Courtesy by biorender.com)



Phytochemicals Used as Natural Candidates Against Colorectal Cancer

Natural candidates from plants have a wide variety of biological applications including anti-inflammatory, antiviral, anti-cancer, anti-bacterial, anti-fungal, etc. and have been classified into major groups based on their chemical structure namely, terpenoids, alkaloids, phenolics, and flavonoids (Buchanan et.al., 2015). Natural products are used to treat many types of cancer directly or indirectly through various drugs. In this chapter, the authors have listed (Table 4) several natural candidates of plant origin that were checked against CRC, their chemical structure and mechanism of action.

Andrographolide on CRC

Andrographolide is the bioactive component of the plant *Andrographis paniculata* (Acanthaceae), and it is a diterpenoid. Andrographolide has anti-inflammatory and anti-cancer properties and the reports have shown that it suppresses NF-κB activation and DNA binding activity (Zhu et al., 2013) (Huang et al., 2019). It may also induce the cell cycle arrest at G0/G1 phase and stimulates lymphocyte proliferation and activation. Hedgehog signalling pathway (Hh) is triggered in colorectal cancer and there are reports on therapeutic effect of andrographolide against CRC. This compound induces antiproliferative effect on HCT-116 cells in a dose dependent and time dependent manner and induces apoptosis through downregulating Hh pathways in CRC. The cytotoxic effect of andrographolide on HCT-116 cells was estimated by MTT assay (Khan et al., 2020). In addition, it has been shown that andrographolide will inhibit human colorectal carcinoma LoVo cell growth by G1–S phase arrest and increased expression of p53, p21 and p16 (L. Lin et al., 2014) (Chao et al., 2013).

Berberine on CRC

Berberine (BBR) is an isoquinoline quaternary alkaloid isolated from *Rhizoma coptidis* (Ranunculaceae). It possesses diverse bioactivities, including antidiarrheal, antibacterial, anti-inflammatory, antidiabetic and antihyperlipidemic effects. Recent studies have shown that BBR exhibits inhibitory effects on a variety of cancers, such as lymphoma, breast, and colorectal cancer. Berberine shows inhibitory effect on the growth of human colorectal adenocarcinoma (LoVo) cells in vitro and in vivo in a time- and dose-dependent manner. BBR inhibits the LoVo cell growth by suppressing cyclin B1, cdc2, and cdc25c proteins. Hence the study supports that BBR can induce cell cycle arrest and apoptosis and may be useful as an alternative therapy for colorectal carcinoma (Cai et al., 2013).

Resveratrol on CRC

Resveratrol is a polyphenol compound extracted from the roots of the medicinal plant *Polygonum cuspidatum* (Polygonaceae) (Buhrmann et al., 2017). This is synthesized as a defence molecule in plants against pathogens like bacteria and fungi. Other plants, such as peanuts, cranberries, grapes, and red wine are rich sources of resveratrol (Huang et al., 2019). Research has shown that resveratrol exerts apoptotic and anti-proliferative effects on CRC by inducing Fas redistribution and inhibiting Wnt signalling. This is going to inhibit invasion and metastasis of CRC. Using Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALT1) and cell lines LoVo and HCT116, the inhibition of Wnt/β-catenin signalling (Ji

et al., 2013). This finding provides evidence to support future use of resveratrol in prevention and treatment of CRC.

Curcumin on CRC

Curcumin is present in turmeric plant, is a hydrophobic polyphenol, the rhizome of the herb *Curcuma longa* (Zingiberaceae) and has a great potential property of suppressing inflammation and inhibiting the growth of neoplastic cells. Many studies have proven that curcumin could be used as a therapeutic agent for CRC through affecting numerous target molecules. Curcumin inhibit proliferation of cancer cells and induce apoptosis by the activation of caspase-3 and mitochondria-mediated pathway in a time and dose dependent manner. It also promotes the expression of Bax, cytochrome C, p53 and p21 but inhibits the expression of Bcl-2 (Su et al., 2006). Both survivin and insulin like growth factor-1 (IGF-1) could lead to inhibition of apoptosis and prolonged survival of colon cancer cells by suppressing the mitochondria-mediated pathway. Curcumin downregulates the expression of survivin and IGF-1 by activating the expression of p53 and reducing tumor necrosis factor-α (TNF-α) levels, leading to activation of apoptotic signal (Li et al., 2015) (Manna et al., 2020). These observations suggest that curcumin may have a possible therapeutic potential in colon cancer patients.

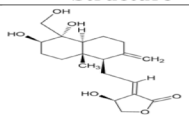
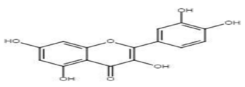
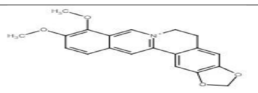
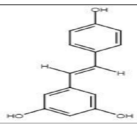
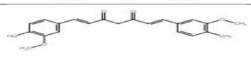
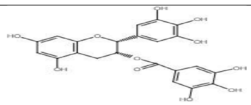
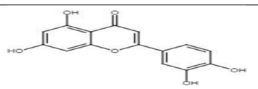
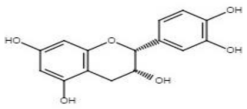
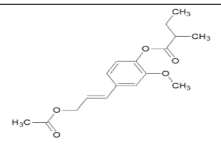
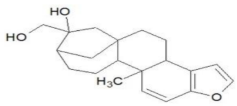
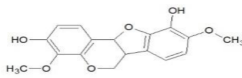
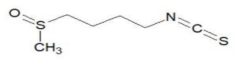
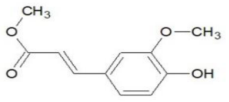
Epigallocatechin Gallate on CRC

Green tea is a globally very popular beverage made from *Camellia sinensis* (Theaceae) leaves. In many Asian countries green tea is used as a traditional medicine to improve blood circulation, digestion and wound healing. While regular intake of green tea consumption is multiple health benefits, treatment with its principle extract has been shown to reduce formation of metachronous colorectal adenomas. A major green tea polyphenol, epigallocatechin-3-gallate (EGCG), has been identified as a potent anti-tumorigenic compound. EGCG can inhibit formation of CRC cancer stem cells (CSC) and subsequently contribute to sensitization against chemotherapeutic agents. Conventional therapeutic drugs are somewhat effective at targeting cancer cells, these agents fail to eliminate CSCs. Considering the safety and anti-cancer profile of natural compounds such as EGCG polyphenolic agents may provide a safe and cost-effective strategy for targeting CSCs and in reducing chemoresistance and tumor recurrence in CRC patients (Yuan et al., 2008). The effect of EGCG on the proliferation of HCT-116 and SW-480 human colon cancer cells studied by MTS assay using phenazine methosulfate (PMS) and observed cell cycle distribution and apoptotic effects. EGCG is proved as most potent antiproliferative agent, and it induces cell cycle arrest in the G1 phase and cell apoptosis. In addition to that EGCG enhances the effects of ginseng compounds during the inhibition of colon cancer cell growth (Du et al., 2012). This observation indicates that green tea could be an effective cancer preventive agent.

Luteolin on CRC

Luteolin is a flavone found in vegetables and fruits such as broccoli, parsley, celery, onion leaves, peppers, cabbages, carrots, apples, and celery (Pandurangan & Esa, 2014), and has beneficial properties including antiinflammatory, anti-allergic, anticancer, and antioxidant activity. It also inhibits cell invasion, metastasis, transformation, and angiogenesis by inhibiting transcription factors, kinase modification and cell cycle arrest and apoptosis. Epigenetic modifications may underlie the anticancer activity

Table 4. The plant natural candidates and their mechanism of actions against CRC cells

Natural Compounds	Structure	Mechanism of action	References
Andrographolide		Suppresses NF- κB activation and DNA binding activity. Hedgehog signalling pathway (Hh) is triggered in colorectal cancer. Inhibit human colorectal carcinoma LoVo cell growth by G1–S phase arrest and increased expression of p53, p21 and p16	(Zhu et al., 2013), (Huang et al., 2019) (Khan et al., 2020) (L. Lin et al., 2014), (Chao et al., 2013).
Quercetin		Suppression of the expression of both cells CACO-2 and SW-620. Inhibits NF- κB and downregulates Bcl-2. Downregulate β-catenin/Tcf transcriptional activity in SW480	(Zhang et al., 2015) (Li et al., 2015). (Park et al., 2005)
Berberine		Inhibitory effect on the growth of human colorectal adenocarcinoma (LoVo) cells by suppressing cyclin B1, cdc2, and cdc25c proteins.	(Cai et al., 2013)
Resveratrol		Apoptotic and anti-proliferative effects on CRC by inducing Fas redistribution and inhibiting Wnt signalling. Inhibit Wnt/β-catenin signalling activity in the cell lines HCT116 and LoVo.	(Buhrmann et al., 2017) (Ji et al., 2013)
Curcumin		Induce apoptosis by the activation of caspase-3 and mitochondria-mediated pathway. Enhances the expression of Bax, cytochrome C, p53 and p21. Inhibits the expression of Bcl-2 and TNF-α.	(Su et al., 2006) (Li et al., 2015) (Manna et al., 2020)
Epigallocatechin gallate		Potent antiproliferative agent, studied in HCT-116 and SW-480 human colon cancer cells and it induces cell cycle arrest in the G1 phase and cell apoptosis. Enhances the effects of ginseng compounds during the inhibition of colon cancer cell growth.	(Du et al., 2012)
Luteolin		Activates the Nrf2 pathway by downregulating DNA methyltransferase (DNMT) and histone deacetylase (HDAC) expression. Modifies Wnt/β-catenin signalling.	(Pandurangan & Esa, 2014)
Procyanidin		Inhibit the PI3k/PKB, and also induces apoptosis in HT 29 and HCT116 cell lines. Downregulates Akt signaling pathway	(Toden et al., 2018) (Choy et al., 2016)
Tripolinolate A		Shows anti-proliferative effect on CRC cells, HCT-15 and SW620, and arrest cell cycle at G2 /M phase in SW620 cells.	(CHEN et al., 2017)
Kahweol		Suppress the viability of HT-29 cell via caspase-3 expression. Attenuate the expression of HSP-70.	(Choi et al., 2015)
Indigocarpan		Shows an anti-proliferative effect by increasing p53, p21 and by decreasing Cyclin B1 and Cyclin D1 in LS174T cells at G2 and Mitotic Phase of a cell.	(Mahajan et al., 2016)
Sulforaphane		Suppression of cell viability in the cell lines H Induces the HCT116 CRC cell cycle arrest at G2and M phase by increasing CDK2, cyclin A and B expression levels at lower level of cdc25C and CDK1T-29 and SW480.	(Hao, 2019) (Gwon et al., 2020)
Methylferulate		Induces the anti-proliferative effect on CRC cells like SW1116 and SW837 by increasing p19 and p27 and by decreasing CDK1 and CDK 2 at synthetic phase and G2 or mitotic phase of the cell	(Abaza et al., 2016)

of luteolin. Recently, Zao et al. demonstrated that luteolin epigenetically activates the Nrf2 pathway by downregulating DNA methyltransferase (DNMT) and histone deacetylase (HDAC) expression.this investigation reported the apoptotic effects of luteolin on human colon cancer cells and elucidating the underlying mechanism involving DNA demethylase, ten-eleven translocation (TET) of the Nrf2 promoter and the relationship between Nrf2 and p53, a tumor suppressor (Kang et al., 2019). Luteolin also reduce oxidative stress, modifies Wnt/β-catenin signalling (Pandurangan & Esa, 2014). There are evidences about the anti-colon cancer effect of luteolin that potentially controls CRC in multiple aspects and can be considered as a natural candidate to treat CRC.

Quercetin on CRC

Quercetin is an important dietary polyphenol found in red onions, apples, berries, citrus fruits tea, and wine. It plays a role in preventing colon cancer through anti-oxidant, anti-inflammatory, antiproliferative, and pro-apoptotic mechanisms. The inhibitory effect of colon cancer cells is influenced by the supplementation of quercetin to the cell lines such as CACO-2 and SW-620 showed the most efficient suppression of the expression of both cells (CACO-2 and SW-620) (Zhang et al., 2015). Quercetin also inhibits NF- κB and downregulates Bcl-2 (Li et al., 2015). Another study reports about quercetin that it reduces nuclear β-catenin and Tcf-4 proteins to downregulate β-catenin/Tcf transcriptional activity in SW480 in a concentration dependent manner. Similarly it inhibits the elevated b-catenin/ Tcf signaling by wild b-catenin gene transfection in HEK293 cells (Park et al., 2005).

Procyanidins on CRC

Proanthocyanidin is a polymer of flavan-3-ol or flavan 3, 4-diol molecules and an important part of human diet found in fruits like apple, maritime pine bark, cinnamon, aronia fruit, cocoa beans, grape seed, grape skin, cocoa and red wines of *Vitis vinifera*. However, bilberry, cranberry, black currant, green tea, black tea, are the other sources of procyanidins. The procyanidins inhibit the PI3k/PKB, and also induced apoptosis in colon cancer. Proanthocyanidin treatment performed in both MSS (microsatellite stable) and MSI (microsatellite unstable) by performing an assay on HT 29 (MSS) and HCT116 (MSI) cell lines. Significantly cellular growth inhibited in both cells by treatment with proanthocyanidins (Toden et al., 2018). Choy et al., showed the effect of procyanidines on human CRC cells by inducing apoptosis and cell cycle arrest, downregulating the Akt signaling pathway. Thus, the fruit and vegetables rich in procyanidins could help to reduce the growth of colon cancer cells (Choy et al., 2016).

Tripolinolate A on CRC

Tripolinolate A (TLA) is derived from halophytic plant *Tripolium vulgare* and has significant *in vitro* activity against proliferation of colorectal cancer HCT-15 and SW620 cells. TLA induced apoptosis in the CRC SW620 cells and significantly arrested cell cycle at G2/M phase. (CHEN et al., 2017)

Kahweol on CRC

Kahweol is a fat soluble diterpene molecule isolated from *Arabica coffee* beans and has antioxidant, anti-inflammatory, and antitumor activities. There are reports about morphological changes and cytotoxic

effect of kahweol in HT-29 cells of colorectal cancer, studied by carrying LDH and MTT assay. Kahweol significantly suppressed the viability of HT-29 cell via caspase-3expression, is a pro-apoptotic factor, and decreased the expression of anti-apoptotic factors like Bcl-2 and phosphorylated Akt and mediates apoptosis. The kahweol attenuate the expression of HSP-70, a heat shock protein that plays a crucial role in kahweol-induced cytotoxicity in H-29 cells. These reports demonstrate that kahweol inhibits CRC by apoptosis process and suppressing HSP70 expression (Choi et al., 2015).

Sulforaphane on CRC

Sulforaphane is a polyphenol, derivative of isothiocyanate found mainly in cruciferous vegetables like broccoli, cabbage, cauliflower, bok choy, kohlrabi, mustard, turnip, radish etc. Sulforaphane showed numerous properties such as, antioxidant, anti-inflammation, anti-tumor, anti-microbial and it promotes apoptosis, also shows epigenetic modulation through histone deacetylase inhibition and microRNA modulation (Nandini et al., 2020). Sulforaphane showed the dose dependent suppression of cell viability in the cell lines HT-29 and SW480 of CRC by arresting cell cycle at G0/G1 phase. The apoptosis rate of SW480 cells were higher than HT-29 (Hao, 2019). Sulforaphane also induces the HCT116 CRC cell cycle arrest at G2and M phase by increasing CDK2, cyclin A and B expression levels at lower level of cdc25C and CDK1 (Liu et al., 2016). Sulforaphane also influence proliferation and mitochondrial function of colorectal cancer cells through nuclear factor erythroid 2-related factor 2 (Nrf2) mediated signalling pathway and p53 axis, studied in HCT116 cell lines (Gwon et al., 2020).

Indigocarpan on CRC

Indigocarpan is also known as pterocarpan, one of the flavone glycoside isolated from *Indigofera aspalathoides* plant. In human colorectal cancer LS174T cells, indigocarpan shows antiproliferative activity by increasing p53, $p21^{WAF-1}$ and cleaving caspase-3 levels, and decreasing PCNA, cyclin D1, cyclin B1 protein levels. It also shows time dependent apoptosis on LS174T cells. Indigocarpan decreases the LS174T cells at their G2 and M phase. Indigocarpan has strong antioxidant, antiproliferative and anti-carcinogenic property indicating its potential to inhibit CRC (Mahajan et al., 2016).

Methylferulate on CRC

Methyl ferulate (MF) is a polyphenol identified in *Tamarix aucheriana*. Methylferulate is well known for its anti-proliferation, anti-oxidation, and apoptosis. It also inhibits the NF-κB DNA-binding activity in CRC and showed a dose dependent antiproliferation of CRC, arrest the cell cycle at S and G2/M phases, induces anti-proliferative effect on CRC cell lines like SW1116 and SW837 by upregulating the cyclin dependent kinase inhibitors such as p19, p21, and p27, and downregulating cyclin-dependent kinases such as CDK1 and CDK2 (Abaza et al., 2016).

CONCLUSION

Colorectal cancer is closely linked to the global cancer-related mortalities worldwide. The present treatment for colon cancer is generally based on using cytotoxic drugs, radiotherapy, chemotherapy,

and surgery, with several side effects. The gut microbiota contain a large population of microorganisms that interact directly with host intestinal cells and it can affect the immunity and metabolic activities in the gastrointestinal tract. Different approaches including prebiotics, probiotics, postbiotics, and fecal microbiota transplantation (FMT) have been used to implement gut microbiome. Modification of the gut microbiota is a promising approach to improve treatment efficacy and minimize adverse effects of CRC therapies. The potential of natural compounds such as flavonoids, alkaloids, or terpenoids for cancer prevention that are used have been widely investigated. So many shreds of evidence supporting that moderate consumption of fruits and vegetables are correlated with decreased risk of CRC. The current therapies available are not sufficiently effective and their efficacy is limited by the side effects of the drugs and/or the development of resistance. Therefore gut microbiome therapy and use of plant natural products have received great attention for colon cancer prevention owing to their various health benefits, noticeable lack of toxicity and side effects.

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Chapter 6
Colorectal Cancer:
Natural Products as a Treatment

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ABSTRACT

Colorectal cancer (CRC) is intently connected to the malignancies and mortalities worldwide. Surgery and chemotherapy are the current clinical treatments for CRC. However, new and productive drugs are instantly required to overcome the occurrence of side effects and emergence of drug resistance. Natural products possess apoptogenic activities and anti-cancer effects against CRC as many natural compounds are well tolerated by the patients and do not cause toxic effects even at high doses. The current research aims to display anti-CRC effects of natural products based on chemical structure such as alkaloids, terpenoids, polysaccharides, polyphenols, and unsaturated fatty acids. Furthermore, drugs derived from natural products used clinically for the treatment of CRC are discussed. This work also highlights natural products with marine origin as a candidate drugs for CRC. This work highlights the importance of natural products as promising sources of lead anti-colorectal medicine.

1. INTRODUCTION

Colorectal cancer (CRC) is the world's third most frequent cancer (after lung and breast cancer) and the fourth-largest cause of cancer death. According to GLOBOCAN data from 2012, 1.6 million new instances of CRC are diagnosed each year, with 694,000 people dying from the disease (Bray et al., 2018). CRC is most common in people over the age of 50 (Krejčí et al., 2021). Colorectal cancer is

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caused by a complex combination of factors, the most important of which are age, family history, gender, geographic location, and personal history (Le Peng et al., 2018; Shen et al., 2018; Center et al., 2009). Smoking and obesity have been identified as risk factors for CRC in previous research. Dietary habits are also a significant influence on CRC. Calcium consumption has been demonstrated to be inversely linked to the risk of CRC; calcium plays a role in CRC immunological prophylaxis by influencing T cell activity (Zhang, X et al., 2016; Keum et al., 2014; Yang et al., 2019). According to MPE (molecular pathological epidemiology) studies, aspirin can reduce the risk of PTGS2-positive CRC and patient death, but not the risk of PTGS2-negative CRC (Benelli et al., 2018). Surgery and chemotherapy are the most common therapies for CRC. Chemotherapeutics can kill cancer cells by generating DNA damage or activating numerous signaling pathways, such as cell cycle arrest, global translation inhibition, DNA repair, and so on (Woods et al., 2013). However, as numerous research have demonstrated, including MPE studies, the treatment success of chemotherapeutic medicines in CRC patients differs depending on the cancer subtype. The main difficulties linked with chemotherapy are cytotoxicity, drug resistance, and unpleasant reactions. Many effective lead compounds for the discovery of novel medications have come from complex and diverse natural sources. Many natural products have shown to be effective in fighting inflammation, viruses, germs, tumors, and other diseases (Oliveira et al., 2017; Miyata et al., 2007).

Colorectal cancer (CRC) being one of the most frequent diseases in humans, and it is intimately linked to global cancer-related deaths. Surgery and chemotherapy are the most common clinical treatments for CRC. However, due to the appearance of side effects and the introduction of new medication resistance, new and more effective medications for CRC treatment are urgently needed. An increasing number of natural items have been shown in trials to have effective anti-CRC properties and may be used as an alternative to chemotherapy in the treatment of CRC. Many natural substances decrease tumor growth by triggering cell cycle arrest or death in CRC cells, resulting in tumor growth inhibition. A so-called innovative application of natural chemicals is a so-called Combination therapy that entails the simultaneous administration of two or more chemicals, such as conventional chemotherapeutics and one or more natural medicines. Even at high concentrations, many natural compounds are well tolerated by patients and do not cause hazardous effects. The interaction of traditional chemotherapeutics with natural products adds a new wrinkle to cancer research and treatment. It could be a promising strategy for achieving gains while limiting the negative effects of traditional chemotherapy. In this chapter, we describe anti-CRC natural products from various sources based on chemical structures such as alkaloids, polysaccharides, polyphenols, terpenoid, and unsaturated fatty acids, and address natural product-derived medications utilized therapeutically for colorectal cancer treatment. Furthermore, natural products with marine origin as a candidate drugs for CRC is also discussed.

2. NATURAL PRODUCTS AS A TREATMENT FOR COLORECTAL CANCER

The use of natural product derived medication for the treatment of infectious disease has made a significant contribution to human health such as penicillin for the treatment of infectious diseases (Rammelkamp et al., 1943), streptomycin for long-term treatment of tuberculosis (Bondarev et al., 1980), a potent anti-inflammatory plant extract paeoniflorin (Zhang, L et al., 2008), the natural plant-derived anti-HIV drug patentiflorin (Zhang, H et al., 2017), cyclosporine which has immunomodulatory properties (Kahan, 1989), lovastatin which has a hypolipidemic effect (Rosenson & Tangney, 1998).

Patients will have better treatment outcomes and a higher quality of life if they use natural items that are well tolerated and have low toxicity. Many chemotherapeutic medicines have been discovered by looking for possible molecules in plants, animals, and microbes, including marine species, and they have been found to have anti-cancer properties against a range of cancers (Singh et al., 2008; Li & Lou., 2018; Angulo et al., 2017; Sharma et al., 2018; Mao et al., 2017).

Natural product-derived medicines have extensive application prospects for the treatment of CRC, according to accumulating evidence from earlier investigations (Johnson & Mukhtar., 2007; Benarba & Pandiella., 2018; Aires et al., 2013). Another study describes the many varieties of fruit and vegetables on proximal and distal colon cancer risk. Proximal colon cancer risk and rectal cancer do not appear to be linked to the consumption of total fruit and vegetable except for brassica vegetables. Consumption of carrots, pumpkin, and apples was found to reduce the incidence of distal colon cancer (Annema et al., 2011).

The use of probiotics and prebiotics to alter the gut microbiota, either alone or in combination appears to be an effective chemopreventive strategy that could have a good impact on inflammation and CRC. Antioxidant supplements alone may not be the greatest therapeutic option; instead, a conventional treatment combined with natural chemicals that activate multiple signal pathways may strengthen the effect of the drug's effective concentration while minimising side effects. Polysaccharides from Ganoderma lucidum extract can boost immunity, while triterpenes from Ganoderma lucidum can boost the production of reactive oxygen species (ROS) in chemotherapeutic agent doxorubicin (Wang et al., 2013; Yue et al., 2008).

Recent research has emphasized the relevance of a combination approach, with some studies claiming that this therapy is more effective than utilizing traditional chemotherapeutic drugs (Singh et al., 2013). The Chou-Talalay combination index can be used to identify whether the combined strategy in the treatment of malignancies is synergistic (increased), antagonistic (reduced), or additive (identical) to their effect on independent administration (Chou & Talalay.,1984). By substituting a well-tolerated natural chemical for a portion of traditional chemotherapeutic medication, the resultant consequence could be a reduction in the patient's toxic burden with a predetermined outcome (Redondo-Blanco et al., 2017).

3. NATURAL COMPOUNDS AS ANTI-CRC DRUGS

Natural products, such as alkaloids, polysaccharides, polyphenols, diterpenoids, and unsaturated fatty acids, have become fruitful sources of new anticancer drugs, and about 50% of currently used anticancer drugs are derived directly or indirectly from natural products (Qiao et al., 2020). Many contemporary anticancer medications are derived from natural sources, such as irinotecan, vincristine, etoposide, and paclitaxel. Streptomyces produces actinomycin D and mitomycin C, while bleomycin is the first marine chemical (Nobili et al., 2009). The continuous discovery of such products has opened up a novel direction for cancer prevention and therapy; the natural product-based drugs used clinically for CRC treatment are discussed and are summarized in Table 1.

3.1. *Alkaloids*

3.1.1. Irinotecan (CPT-11)

Irinotecan is a water-soluble camptothecin derivative that slows DNA replication and RNA synthesis by inhibiting DNA topoisomerase I (Font et al., 2002). CPT-11 has been proven to have an interesting anticancer efficacy against metastatic colorectal cancer, despite its use as first-line therapy or second-line therapy following fluorouracil treatment failure (mCRC). CPT-11 has been used as a standard treatment for CRC all over the world, and clinical trials have shown that when combined with 5-fluorouracil (5-FU)/ formyltetrahydrofolate (CF) for the treatment of advanced mCRC, CPT-11 has a superior anti-tumour impact (Douillard et al., 2000; Conti et al., 1996; Rougier et al., 1997).

3.1.2. SN38

SN38, the active analogue of irinotecan, has been shown to limit the growth of a range of malignant cells (Al-Kasspooles et al.,2013). The reduction of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1 alpha expression is primarily responsible for SN38's antiangiogenic effect. SN38 has two inhibitory effects: it inhibits endothelial cell proliferation and lumen creation, as well as glioma cell angiogenic activity. At a dosage of 0.01 M, Kamiyama H discovered that SN38 can specifically block three-dimensional tubular structure development and endothelial cell proliferation (Kamiyama et al., 2005). Even though CPT-11 and SN38 have broad anti-tumour effectiveness against a variety of cancers, CPT-11 and its analogues are associated with considerable toxicity, including cholinergic syndrome, neutropenia, and delayed diarrhea (Iihara et al., 2019; Hamano et al., 2019; Saliba et al., 1998).

3.2. Polyphenols

3.2.1. Resveratrol

Resveratrol is a polyphenolic chemical produced by plants in response to pathogens such as bacteria or fungi; it is abundant in peanuts, grapes, and red wine. Previous research suggests that resveratrol functions as the silent information regulation 2 homolog 1 (SIRT1) in the regulation of organisms' average life cycles, and that it has potent inhibitory effects on hepatocellular carcinoma, breast cancer, gastric cancer, leukaemia, and other tumour cells (Puissant et al., 2010; Nakagawa et al., 2001; Mouchiroud et al., 2010; Bishayee et al., 2010; Rao et al., 2009). Resveratrol has been demonstrated to have anti-proliferative and apoptotic effects on CRC cells by inducing Fas translocation and inhibiting Wnt signalling (Ji et al., 2013). The grape seed extract was found to inhibit the PI3K pathway, causing apoptosis and suppressing the survival of CaCo-2 cells by Engelbrecht et al. (Engelbrecht et al., 2007).

3.2.2. Curcumin

Curcumin, a phenolic phytochemical produced from the rhizome of Curcuma longa, has anti-cancer properties as well as growth inhibitory properties in cancer cells. Curcumin reduces cancer cell proliferation and promotes death in cancer cells via p21-mediated cell cycle arrest, according to several studies. Cancer cells lacking p21 are more susceptible to apoptosis in response to many cytotoxic treatments.

The goal of this work was to see if p21 status influenced curcumin-induced cytotoxicity in cultures of HCT-116 human colon cancer cells. In an MTT cell viability assay, curcumin killed wild-type HCT-116 cells in a dose- and time-dependent manner. Furthermore, curcumin had an equal cytotoxic effect in both p21 (+/+) and p21(-/-) HCT-116 cells, demonstrating that curcumin-induced cytotoxicity was not p21-dependent. Primary cultures of human dermal fibroblasts were less responsive to lower dosages of curcumin than HCT-116 colon cancer cells, implying a degree of selectivity towards cancer cells. Cell death in curcumin-treated cultures of p21(+/+) and p21(-/-) HCT-116 cells was related to a reduction in pro-caspase-3 and PARP-1 cleavage, both of which are indicative of apoptosis, according to Western blot analysis (Ruan et al., 2019).

3.3. Polysaccharides

3.3.1. PSK (Krestin)

PSK (Krestin) is a protein-bound polysaccharide K isolated from Coriolus Versicolor with a molecular weight of 100 kDa and a protein concentration of 18–38%. PSK dramatically reduced mortality associated with dextran sodium sulfate-induced colitis and suppressed the development of CRC, according to Tsutsumi et al. implying that it has dual anti-inflammatory and anti-CRC properties. PSK's anti-cancer activity is mediated through many routes, including recovery from immunosuppression generated by TGF- and anti-tumour immune responses, and improved chemotherapy efficacy by inducing apoptosis and blocking cancer cell metastasis (Maehara et al., 2012; Tsutsumi et al., 2011).

3.3.2. Fucoidan

Fucoidan is a sulfated polysaccharide isolated from brown seaweeds that have been shown to have a variety of biological functions (Ikeguchi et al., 2011). Fucoidan promotes apoptosis in HT-29 and HCT116 cells, according to a prior study (Kim et al., 2010). Low-molecular-weight fucoidan has been shown to have strong effectiveness against CRC in people in double-blind, randomised clinical trials with few adverse effects (Tsai et al., 2017).

3.4. Unsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) are abundant in marine microalgae (> 80%), primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Go et al., 2016). EPA and DHA are beneficial against CRC, breast cancer, and pre-existing adenocarcinoma because they block essential angiogenic factors such as platelet growth factor, VEGF, and endothelial cell growth factor. The growth of CRC cells has been demonstrated to be inhibited by DHA and EPA (in the form of acid and phospholipids), and PUFAs have been found to have a larger growth-inhibitory impact in the HT-29 cell line than in the Caco-2 and DLD-1 cell lines (Nauroth et al., 2010; Hossain et al., 2008) .

3.5. Terpenoids

Andrographolide is a diterpenoid that is the main bioactive component of the plant Andrographis paniculata, which has been used for thousands of years in Asia as traditional herbal medicine. Andrographolide

has been shown to inhibit NF-kB activation and DNA binding activity (Zhu et al., 2013; Hidalgo et al., 2005), and as a result, it has a variety of biological actions, including anti-inflammatory (Shen et al., 2013; Lee et al., 2011) and anti-cancer characteristics (Chao et al., 2013; Wang et al., 2016). By binding andrographolide to the BAX protein and upregulating BAX expression, a combination treatment of andrographolide and 5-FU can trigger apoptosis in HCT116 cells (Xu et al., 2015). Xu et al. demonstrated the safety and efficacy of a combination of andrographolides and capecitabine in elderly individuals with locally advanced CRC.

3.6. Cannabinoids

For millennia, Chinese medicine has relied on the benefits of cannabis (Cannabis sativa) to alleviate pain and hallucinations. Flavonoids, terpenoids, and more than 60 types of cannabinoids are among the bioactive compounds found in this plant (Chakravarti et al., 2014; Ware et al., 2003). Cannabinoids are routinely utilized in the palliative treatment of cancer patients who are undergoing chemotherapy (Martínez-Martínez et al., 2015). Research, however, suggests that cannabinoids could be used in anti-cancer therapy as well (Hermanson & Marnett, 2011). Cannabinoids have anticancer effects in vitro and in vivo in animal models through a variety of mechanisms, including inducing apoptosis in tumour cells, inhibiting proliferation and angiogenesis, and inhibiting tumor cell migration (Cianchi et al., 2008; Izzo et al., 2009; Aviello et al., 2012; Pisanti et al., 2013). The psychoactive D9-tetrahydrocannabinol (D9-THC), which inhibits tumor growth as well as several other cannabinoids, is the main bioactive molecule in this plant. D9-THC and other naturally occurring cannabinoids, synthetic cannabinoid agonists, and endocannabinoids have in vitro anticancer effects in lung, glioma, thyroid epithelioma, lymphoma, skin cancer, uterine carcinoma, breast cancer, prostate carcinoma, pancreatic carcinoma, and neuroblastoma, according to several preclinical studies (Sarfaraz et al., 2008).

3.7. Allylsulfates

Allylsulfates, which are found in garlic, onion, and shallot, as well as chive and leek (Alliaceae), are the second group of organosulfates. Diallyl trisulfide (DTS), which reduces proliferation and causes death in human colon cancer cells (HCT-15 and DLD-1) by oxidative alteration of beta-tubulin (Hosono et al., 2005), is one of the most important bioactive chemicals in this group of vegetables. In a mouse CT-26 cell also implant model in vivo, diallyl trisulfide reduces the formation of mice colon tumors (Wu et al., 2011). In human primary CRC cells, it also causes apoptosis and promotes the generation of reactive oxygen species (ROS) (Yu et al., 2012).

Drinking herbal tea may lower the incidence of distal colon cancer due to its antiproliferative and anti-angiogenic properties. Melissa officinalis (MO) hot water extract had the greatest anticancer effect on CRC cells. Since, MO reduced cell proliferation, induced cell cycle arrest at the G2/M phase, triggered caspase-dependent apoptotic cell death, and inhibited cell migration ability by modulating the epithelial−mesenchymal transition in HCT116 CRC cells, implying that the practice of drinking herbal tea inhibits the growth of CRC (Kuo et al., 2020). Graviola, either alone or in combination with Cranberry, might be utilized as a natural anti-proliferative agent and hence as an anti-tumor agent against colorectal cancer cells. Furthermore, the cytotoxic impact of Graviola and/or Cranberry was tested on colorectal cancer cell lines (Caco2) as Graviola and/or Cranberry caused Caco-2 cell cycle arrest at the G2/M phase and stopped cells from entering the mitotic phase (El-Khashab et al., 2019).

3.8. Ganoderma Lucidum (Fungus)

Ganoderma lucidum (GLC) is the type of mushroom used in japan, china and several other Asian regions due to its significant anti-inflammatory and immunomodulatory effects. GLC also finds its use in cancer therapeutics. Bioactive components found in GLC are polysaccharides and triterpenoids. Anti-tumor and immunotherapeutic activities have been discovered in the GLC extract. Increased expression of NKG2D and natural cytotoxicity receptors has been found to boost NK cell cytotoxicity. (NCR), enhanced intracellular MAPK phosphorylation and perforin promotes the secretion of granulysin, which could explain the possibility of the chemical basis of GLC extract's anticancer actions in humans. In several human tumour cell lines, Ganoderma lucidum causes cell cycle arrest and apoptosis. The constant activation of transcription factors AP-1 and nuclear factor kappa B is one of the features of highly metastatic tumour cells (NFkB). GLC has been demonstrated to block these factors, resulting in the suppression of urokinase plasminogen activator (uPA) and its uPAR receptor expression. Anti-inflammatory, hypoglycemic, anti-tumor, and immunostimulatory polysaccharides derived from Ganoderma lucidum (GLP) limit the generation of reactive oxygen species (ROS) and reduce oxidative DNA damage. Polysaccharides increased caspase-8, caspase-3, and Fas in HCT116, causing apoptosis (Liang et al., 2014). GLP also reactivated mutant p53 in the HT29 and SW480 colorectal lines, either alone or in combination with 5-FU (Jiang et al., 2017). GLC contains almost 200 pharmacologically potent triterpenoids, some of which are known as ganoderic acids. Farnesyl protein transferases, which are required for the activation of the Ras oncoprotein responsible for cell transformation, are inhibited by ganoderic acids A and C (Chang et al., 2014; Sliva, 2003; Miyazaki et al., 1981; Lee et al., 1998). In the colon carcinoma xenograft model, the triterpene extract (GLT) lowers the proliferation of human HT-29 colon carcinoma cells and slows tumour growth. This action is linked to cell cycle arrest at the G0/G1 phase transition and apoptosis induction. In cell lines in the xenograft model, GLT causes the development of autophagous vacuoles and enhances the expression of Beclin-1 and LC-3 proteins. Inhibition of p38 MAPK (mitogen-activated p38 protein kinase) causes autophagy (Thyagarajan et al., 2010).

3.9. Flavonoids

Flavonoids are the most prevalent class of bioactive molecules found in plants, and they are critical to their morphology and function. Flavonoids are pigment elements found in plant stems, leaves, flowers, and seeds. They help plants grow and reproduce, as well as protect them from UV rays and microbial illnesses. Flavonoids are powerful antioxidants that can protect cells from the development of cancer. They also have phytoestrogenic, anti-diabetic, anti-inflammatory, antibacterial, and antiviral properties (Kumar & Pandey., 2013). Some flavonoid compounds are listed below

3.9.1. Epigallocatechin

Epigallocatechin-3-gallate (EGCG) is the main representative of polyphenols found in green tea, and its anticancer effects have been validated by numerous in vitro, in vivo, and clinical experiments. EGCG inhibits a number of important signalling pathways. It inhibits CRC cell proliferation and migration by blocking the TF/VIIa/PAR2 signalling pathway (Protease-Activated Receptor 2), which promotes ERK1/2 phosphorylation and, ultimately, the activation of proinflammatory NF-kB. Reduced NF-kB transcription factor activity increases caspase-7 expression while decreasing MMP-9 (matrix metalloproteinase 9)

expression. EGCG also acts as an epigenetic regulator, assisting in the degradation of DNMT3A (DNA methyltransferase 3A) and HDAC (histone deacetylases) via the ubiquitination process in colorectal cells susceptible to methylation (Singh et al., 2011; Zhou et al., 2012; Khan et al., 2015).

3.9.2. Apigenin

Apigenin (40, 5, 7-trihydroxyflavone) is a flavone present in several foods, including Chinese cabbage, parsley, paprika, garlic, and celery. In vitro, it has chemopreventive and cytostatic characteristics, lowers angiogenesis, inhibits colorectal cell proliferation, cell arrest, and promotes apoptosis (Engelmann et al., 2002). Apigenin enhances the expression of proapoptotic proteins NAG-1 and p53, as well as the cell cycle inhibitor p21, in colorectal cells in vivo and in vitro, reducing the burden and number of intestinal tumours (Zhong et al., 2010). Apigenin is an ABC receptor inhibitor that promotes the efflux of a chemotherapeutic drug in colorectal epithelial cells, hence increasing its bioavailability (Katayama et al., 2007). CD26 is a membrane protein that controls growth and metastasis pathways and is typically downregulated in several forms of cancer, including CRC. Apigenin boosts the number and activity of CD26 in the colorectal lines HT- 29 and HRT-18. Apigenin was reported to enhance CD26 activity when combined with irinotecan (Lefort et al., 2011).

3.9.3. Chrysin

Another polyphenolic flavone found in honey, propolis, chamomile, and martyrs (Passiflora caerulea) is chrysin (5, 7-dihydroxyflavone). Chrysin has anti-tumor properties in a variety of tumour lines and appears to be a natural chemopreventive drug. In HCT116, DLD-1, and SW837 cells, chrysin causes cell apoptosis. This chemical also stimulates TNF and AHR signalling pathways and upregulates Tumor necrosis factor (Tnf) “a” and “b” genes (Ronnekleiv-Kelly et al. 2016). A study on the colorectal line SW480 found that chrysin causes a cell cycle halt at the G2/M transition and that combining it with apigenin doubled the impact and slowed tumour development (Wang et al., 2004). Chrysin also protects cells against induced cisplatin toxicity in vivo in a mouse model, which is linked to oxidative stress suppression via p38MAPK, p53, and apoptosis (Khan, R et al., 2012).

3.9.4. Kaempferol

Propolis, grapefruit, black tea, and broccoli all contain kaempferol, a flavonol. Kaempferol showed anticancer efficacy in colorectal tumour lines. Kaempferol increases apoptosis and CDK2, CDK4, and Cdc2 activity in the HT-29 cell line, resulting in cell cycle arrest in the G1 and G2/M phases (H. Lee et al., 2014; Cho et al., 2013). In the HT-29 cell line, kaempferol increased chromatin condensation, DNA fragmentation, and the number of early apoptotic cells. It also enhanced cleaved caspase-9, caspase-3, and caspase-7 levels. These methods suggest that kaempferol induces HT-29 cell apoptosis via processes linked with the activation of cell surface death receptors and the mitochondrial pathway (S. Lee et al., 2014). It also promotes apoptosis in SW480 and DLD-1 colorectal cell lines, with TRAIL co-treatment producing a greater effect (TNF-associated apoptosis-inducing ligand, apoptosis-inducing ligand), and kaempferol sensitises cells to TRAIL treatment (Yoshida et al., 2008).

3.9.5. Quercetin

Quercetin is a common flavonol found in apples, onions, and a variety of other vegetables and fruits. Quercetin reduces the production of RASA1 (RAS p21 protein activator) and hence prevents RAS activation in human colon cancer cells Colo-205, Colo-320HSR, Colo-201, LS-174, and WiDr (Ranelletti et al., 2000). Similarly, quercetin and kaempferol sensitise SW-620, HT-29 (both synergistic effects), and Caco-2 (additive effect) cells to TRAIL, leading them to die (Psahoulia et al., 2007). Overexpression of COX-2 and enhanced production of reactive oxygen species (ROS) were reported in quercetin-treated HT29 cells (Raja et al., 2017). In an experimental in vivo metastasis model, quercetin also significantly reduced lung metastasis of colon cancer CT26 cells. Quercetin inhibited CT26 cell migration and invasion via regulating the production of matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs). As a result, quercetin may be an effective treatment for metastatic CRC (Kee et al., 2016).

3.10. Terpenes

Terpenes are a class of chemical molecules that are ingredients of essential oils. Terpenes are volatile smells found in the leaves, fruits, flowers, rhizomes, and roots of plants. Terpenoids are oxidised terpenes such as limonene, vitamin A, b-carotene, and steroids. Individual terpenes are discussed more below.

3.10.1. Geraniol

Geraniol is best recognised as an essential oil component; it can be found in rose oil, palmarosa oil (Cymbopogon martinii, palmarosa), or citronella oil, and it is also present in geraniums (Pelargonium). Geraniol is a possible chemopreventive agent in the diet. Its chemopreventive activity was tested in male Wistar rats with colon tumours generated by dimethylhydrazine in vivo. The number of total aberrant crypt foci in the distal colon reduced dramatically, whereas the level of apoptosis in the distal colon increased significantly (Vieira et al., 2011). Geraniol boosted apoptosis in the Caco-2 cell line in vitro when combined with 5-FU. Combining 5-FU with xenografts of the TC118 cell line resulted in tumour reductions of up to 83 percent (Carnesecchi et al., 2004).

3.10.2. Artesunate

Artesunate is a sesquiterpene artemisinin derivative discovered in the traditional Chinese wormwood annual plant (Artemisia annua), which is used to cure fever and rheumatism. Artemisinin, the main active ingredient, was found and isolated in the 1970s and has historically been used to treat malaria because it increases reactive oxygen species (ROS) in the Plasmodium parasite. The other substances aren't on the WHO list. Clinical research data is currently scarce. Artesunate also has antiproliferative properties, making it a potential anticancer agent. Artesunate is cytotoxic to HCT116 colorectal cancer cells, causing cell cycle arrest in the G1 phase via decreasing cyclin D1 expression and raising p21 expression. In co-therapy with oxaliplatin, artesunate produces higher ROS of artesunate on tumour immunosuppression, which is the main source of inefficient tumour treatment. (Liu et al., 2011; Meshnick et al., 2002). Another study sought to evaluate the effect of artesunate on tumour immunosuppression, which is the primary cause of unsuccessful tumour treatment.

3.11. Ginko biloba

The extract of Ginkgo biloba includes more than 60 biologically active compounds, the most important of which are turpentines, flavonoids, carboxylic acids, and L-ascorbic acid. Ginkgo biloba EGb 761 extract suppresses HT-29 cell line development, and its action may be connected to increased caspase-3 activity, enhanced p53 expression, and decreased bcl-2 expression (Chen et al., 2011). EGb was also examined in Phase II clinical trials in combination with 5-FU, and the study's authors would advocate this method as second-line treatment in patients with metastatic CRC (Hauns et al., 2001). On the contrary, the National Toxicology Program conducted a 2-year gavage study on one Ginkgo biloba leaf extract in 2013 and determined that there was high evidence of carcinogenic activity in mice based on increased incidence of hepatocellular carcinoma and hepatoblastoma (National Toxicology Program, 2013).

Table 1. Natural compounds and their derivatives as anti-CRC drugs

Natural products	Source	Chemical class	Mechanism
SN-38	Camptotheca acuminata (bark)	Alkaloids	Anti-proliferation
Resveratrol	Peanuts, blueberries, grapes, mulberries.	Polyphenol	Apoptosis, anti- proliferation
Curcumin	Curcuma longa(turmeric)	Polyphenol	Apoptosis, anti-angiogenesis, cell cycle arrest
PSK	Trametes versicolor(fungi)	Polysaccharides	Apoptosis, anti- proliferation
Fucoidan	Brown seaweed	Polysaccharides	Apoptosis, anti- proliferation
Andrographolide	Andrographis paniculata	Diterpenoid	Apoptosis, anti-proliferation, cell cycle arrest
Cannabidiol	Cannabis sativa	Cannabinoids	chemo preventive effect from oxidative damage, Apoptosis, anti- proliferation
Diallyl trisulfide	Garlic	Allylsulfates	Apoptosis, anti- proliferation
Everolimus	Bacterial	Macrolide	Anti-Angiogenesis, Anti-Metastasis
Irofulven	Fungi	Sesquiterpene	Anti-Proliferation
Epothilone D	Bacterial	Macrolide	Anti-Proliferation
Mitomycin C	Streptomyces	Ethyleneimines	Anti-Proliferation, Cell cycle arrest

4. NATURAL PRODUCT-BASED DRUGS FOR COMBINATION CHEMOTHERAPY

CRC that has spread throughout the body is known as metastatic CRC (Winawer et al., 1997; Horita et al., 2012; R. Lee et al., 2019; Ellebaek et al., 2012). Irinotecan treatment has been shown in earlier clinical trials to significantly improve survival rates and decrease the occurrence of adverse events in patients with advanced mCRC (Cunningham et al., 1998). Irinotecan has been considered as a standard chemotherapeutic agent since then, particularly in patients with advanced mCRC who had failed to respond to 5-FU treatment in the early stages of the disease. Irinotecan is the backbone of combination chemotherapies for metastatic CRC, including FOLFIRI (levoleucovorin (LV) and 5-FU with irinotecan), IROX (irinotecan plus oxaliplatin) and XELIRI (capecitabine plus irinotecan).

4.1. FOLIFRI

One of the current standard chemotherapy regimens for advanced CRC is FOLFIRI, a combination therapy comprising of levoleucovorin, 5-FU, and irinotecan., In the study by Tournigand et al, the objective response rate obtained with FOLFIRI as the first-line therapy (consisting of 200 mg/m2 l-LV or 400 mg/m2 dl-LV as a 2 h infusion, and 180 mg/ m2 irinotecan administered as a 90-minute infusion in 500 mL of 5% dextrose, followed by 400 mg/m2 FU and a 46 -h infusion of 2400 mg/ m2 FU for two cycles, with the dose being increased to 3000 mg/m2 from cycle 3 in case of no toxicity, repeated every 2 weeks) was 56%.Sastre J et al. have administered the FOLFIRI regimen to Patients with advanced CRC who had failed treatment with 5-FU or FOLFOX (oxaliplatin and fluorouracil plus formyltetrahydrofolate) were given the FOLFIRI regimen, and the results were satisfactory: 8.3 per cent complete response rate, 20.8 per cent partial efficiency, and 29 per cent objective efficiency. Mucositis, nausea, vomiting, and gastrointestinal toxicity are the most common side effects of FOLFIRI therapy (Tournigand et al., 2004; Sastre et al., 2003). When used in conjunction with FOLFIRI, antibody-based medicines like panitumumab and bevacizumab have been found to improve the safety and efficacy of mCRC treatment (Xie et al., 2014; Liu et al., 2015; Holch et al., 2019).

4.2. IROX

Oxaliplatin (OXA), a platinum-based medication, creates a cross-link with DNA, preventing it from replicating and transcribing (Woynarowski et al., 1998). In vitro investigations have revealed that OXA suppresses the development of colorectal cancer cell lines resistant to cisplatin and carboplatin (Rixe et al., 1996). Several clinical phase I/II studies (Wasserman et al., 1999; Goldwasser et al.,2000; Bajetta et al., 2004; Timotheadou et al., 2005) have demonstrated the efficacy of IROX (irinotecan plus OXA) in the treatment of CRC. Following the failure of 5-FU therapy, Haller et al. found that IROX therapy (85 mg/m2 OXA, intravenous infusion for 120 minutes, and 200 mg/m2 irinotecan, intravenous infusion for 30 min or 90 min every three weeks) is more effective than irinotecan alone (Haller et al., 2008). IROX treatment, however, was associated with a higher incidence of grade 3–4 diarrhoea (28 per cent against 23 per cent) and severe neuropathy (5 per cent versus 0 per cent) as compared to irinotecan alone (Sobrero et al., 2009). The incidence of vomiting, diarrhoea, nausea and febrile neutropenia in individuals treated with IROX was shown to be considerably higher than in those treated with FOLFOX (Goldberg et al., 2004). IROX is recommended whenever patients are intolerant to 5-FU, demonstrating that it is a viable second-line treatment option for these advanced CRC patients.

4.3. XELIRI

In the treatment of CRC, capecitabine, a highly potent oral fluoropyrimidine, is a promising alternative to 5-FU (Patt et al., 2007). Capecitabine has a higher response rate and better safety than 5-FU/LV (Rea et al., 2005; Shin et al., 2008). Recent clinical trials have indicated that the XELIRI combination (capecitabine plus irinotecan) as a second-line treatment for patients with advanced CRC has definite efficacy and safety (Hoff et al., 2001; Van Cutsem et al., 2001). In 2018, Xu et al. conducted a clinical phase III trial (NCT01996306) with a modified XELIRI (mXELIRI)-AXEPT regimen. mXELIRI (200 mg/m2 irinotecan intravenously on day 1, plus 800 mg/m2 capecitabine orally twice daily on days 1–14, repeated every 21 days) has been reported to have highly satisfactory results when compared to FOL-

FIRI: the median survival time of patients in the mXELIRI group was 16.8 months, while the median survival time of those in the FOLFIRI group was 15.4 months, with a lower probability of neutropenia which indicates mXELIRI can be used as a potential substitute for FOLFIRI, and as a routine second-line therapy for mCRC patients, hence giving a new treatment option for mCRC patients (Xu et al., 2018).

5. ACTION MECHANISM OF NATURAL PRODUCTS BASED DRUGS ON CRC TREATMENT

Natural product-derived medicines have been increasingly employed for cancer therapy in recent years because of their diverse sources, improved bioactivities, and reduced toxicity. Natural product-derived medicines can have anticancer effects by inhibiting proliferation, invasion, apoptosis, autophagy and angiogenesis, all of which are common in human malignancies. Here, the main function of natural product-based drugs against CRC with a mechanism based foundation is generalized.

5.1. Proliferation

In proliferation based regulation, checkpoints closely govern the cell cycle to ensure that cells reproduce in sequential and appropriately orientated stages; the dysregulation of the cell cycle can result in aberrant growth of cancer cells. Many natural compounds have been found to limit cancer cell growth by regulating mitosis and the cell cycle, making them valuable potential alternatives for chemotherapy medicines (Amin et al., 2015).

5.2. Adhesion

Adhesion, migration, invasion of cancer cells, and degradation of the extracellular matrix (ECM) surrounding the target organ are all part of the metastasis process which is one of the most severe characteristics of cancer, and it influences the prognosis and clinical stage of the illness. TGF-/Smad and JAK2/STAT3 signaling pathways are activated during tumor development, progression, and metastasis (Ondroušková et al., 2016; Lin et al., 2019; Liu et al., 2014; Wang et al., 2014).

5.3. Apoptosis

Cell division or cell death maintains the cell mechanism. Cells commit suicide when they are no longer required by initiating an intracellular death mechanism. This process is known as programmed cell death or apoptosis. Apoptosis is classified into two pathways such as intrinsic and extrinsic. The intrinsic route or mitochondrial pathway can initiate the caspase cascade, which results in apoptosis via the release of cytochrome C while the extrinsic route starts apoptosis by activating cell death receptors (DRs) on the cell surface, such as FasL/CD95 L and TRAIL (Kroemer et al., 2007; Fulda et al., 2006).

5.4. Autophagy

Autophagy, also known as type II programmed cell death, is a conserved catabolic process that uses autophagosomes to remove excess long-lived proteins, damaged organelles, and invading infections.

Table 2. Natural products with anti-proliferative effect on colorectal cancer cells

Compound	Mechanism
Lawsonaringenin	Downregulate β-catenin and c-Myc
Ribonucleic acid fraction	Increase p21 and p27, decrease Cyclin D1 and Cyclin A
Ent-kaur-2-one-16β,17-dihydroxy-acetone- ketal	Increase p21, decrease Cyclin D, CDK2 and CDK4
Extracts of *Iberis amara*	Decrease Cyclin A2, Cyclin D3, CDK2, CDK4 and CDK6
Kahweol	Decrease Cyclin D1
Indigocarpan	Increase p21, decrease Cyclin B1 and Cyclin D1
Sulforaphane	Increase CDK1, CDK2, Cyclin B and WEE1, decrease cdc 25C and cyclin A
Methylferulate	Increase p19 and p27, decrease CDK1 and CDK2
Yuanhuacine	Increase p21

Autophagy can be triggered in response to a variety of cellular stressors, such as hypoxia, endoplasmic reticulum stress, ROS deposition, and pharmacological stimulation (He et al., 2009; Yorimitsu et al., 2007; Yang et al., 2019).

5.5. Angiogenesis

Angiogenesis is another natural physiological process that involves endothelial cell migration and morphogenesis during revascularization and delivers oxygen and nutrients to tissues. Extracellular factors such as interleukin-8 (IL-8), tumor necrosis factor (TNF), and platelet-derived growth factor (PDGF) are also involved in the process of angiogenesis, as are VEGF and its receptor. Conferone, an active compound derived from Ferula plants, has been found to limit HT-29 cells' angiogenic potential by controlling the production of VEGF and the growth factors angiopoietin-1 and -2.(Bielenberg et al., 2015; Cheraghi et al., 2016; Sun, 2012).

Some natural products regulating proliferative, invasive, apoptotic and autophagy mechanisms on CRC are tabulated as:

6. MARINE-DERIVED ANTI-COLORECTAL CANCER NATURAL PRODUCTS

Secondary metabolites from the largely unexplored marine environments have proven to be significant sources of potential medicines. Marine populations serve as a repository for novel bioactive metabolites with a wide range of chemical configurations. Advanced technology and extensive research on marine natural products have led to the discovery of a new generation of anticancer drugs currently used in clinical trials. Marine has a lot of potential for discovering novel things that can help with cancer prevention and treatment. Given the enormous potential of marine natural product scaffolds, there is a growing interest in leveraging their diversity and complexity for rational drug development (Newman & Cragg, 2014). The Caribbean sponge (Cryptotethya crypta) was the first marine organism to be chemically studied in-depth (Bergmann & Feeney, 1950) and substantial phytochemical research on pure chemicals from this organism was conducted between 1950 and 1960, prior to the discovery of cytosine arabinoside

Table 3. Natural products with anti-migration and anti-invasion effect on colorectal cancer cells

Compound	Mechanism
α-Hederin	Suppress EMT and JAK2/STAT3
Tea Polysaccharide	Decrease Cyclin D1, MMP-2 and MMP-9
Curcumin	Inhibit FAK/Src, STAT3, Erk and Akt pathways
Esculetin	Target Axin2/Ecadherin axis
Luteolin	Inhibit CREB1 and block EMT
Cairicoside E	Inhibit the EMT through down-regulation of AQP5 and suppression of p-Smad2/3
Resveratrol	Inhibit FAK activity

(ara-C) (Schwartsmann, 2000; Bergmann & Feeney, 1951; Bergmann & BURKE, 1955). In addition, some marine organisms have been studied for cancer control (Fsulkner, 2000; Faulkner, 2000), including microflora (bacteria, actinobacteria, cyanobacteria, and fungi), microalgae, macroalgae (seaweeds) (Sithranga Boopathy & Kathiresan, 2010), invertebrate animals (Rinehart, 2000) sponges, soft corals, sea fans, sea hares, nudibranchs, bryozoans, tunicates, and others (White et al., 2014). Alkaloids, carotenoids, terpenoids, anthraquinones, pentapeptide, quinonoids are some potential secondary metabolites obtained from marine natural products that exhibited anti-oxidant, anti-tumor activities.

Calothixins, salternamide A, 6-bromoisatin, peridinin, sepholenol, sepholenone, physcion, caldoramide, mazamine-A derived from natural sources are some examples that have proven effective in inducing apoptosis, cell cycle arrest, anti-proliferation. Basic information of some marine-derived anti-colorectal cancer natural products is given as:

7. ROLE OF MICROBIAL PRODUCTS IN SUPPRESSING COLORECTAL CANCER

7.1. Butyrate

Butyrate suppresses CRC invasion and proliferation while also promoting cancer cell death. Colon bacteria create short-chain fatty acids (SCFA) such as acetic acid, propionic acid, and butyric acid by breaking down undigested food fibres and starches (van de Wouw et al., 2018). SCFA's aerobic glycolysis supplies colon cells with their primary energy source (Wang et al., 2019), as well as contributing to the host intestine's immunity and metabolism. SCFA content reduces considerably in CRC patients' plasma, indicating that a drop in SCFA promotes CRC growth (Yusuf et al., 2018).

Butyrate is the most researched short-chain fatty acid, and it is primarily produced by two families of human colon firmicutes, ruminococcaceae and lachnospiraceae, via glycolysis from hydrocarbons (Louis et al., 2017). Butyrate suppresses cancer cell multiplication while causing cell death as a histone deacetylase (HDAC) inhibitor (Medina et al., 1997). Butyrate is oxidised by mitochondria in normal colon cells and converted to energy via the tricarboxylic acid cycle (TCA cycle) or cytosolic acyl-coenzyme A. (CoA). Cancer cells can change their metabolic modes even when exposed to oxygen, and they prefer to use the glycolytic pathway rather than the oxidative phosphorylation (OXPHOS) pathway to convert absorbed glucose into lactate (Koppenol et al., 2011). The Warburg effect pathway has been

Table 4. Natural products inducing apoptosis in colorectal cancer cells

Compound	Mechanism
Zerumbone	Induce ROS, activate caspase-3/8/9 and downgregulate Bcl2
Alkylresorcinols	Decrease Bcl2 and XIAP, increase PUMA, cytochrome C, cleaved caspase-9 and -3
Quercetrin	Upregulate Bax, caspase-9, caspase-3 and Apaf-1
Pteisolic acid G	Downregualte NF-κB p65 activity, stimulate p53 and promote ROS production
Oblongifolin C and guttiferone K	Increase cleavage of caspase-3, PARP and JNK phosphorylation and enhance cellular ROS production
Cardol	Increase caspase-3, caspase-9, cleavage of pro-caspase-3 and pro-caspase-9, PARP and ROS
Cuminaldehyde	Activate caspase-3 and -9
BG-4	Reduce Bcl-2, increase Bax and caspase-3
Deoxyelephantopin	Activate caspase-3 and PARP cleavage
Isoledene	Increase ROS, caspase-8, -9 and -3, upregulate Bid, Bim and cytochrome C, downregulate Bcl-2, Bcl-W, survivn, xlAP and HSPs pro-survival proteins
Gambogic acid	Activation of JNK signaling pathway
Hederagenin	Increase ROS, up regulate Bax and decrease Bcl-2, Bcl-xL, procaspase-9, procaspase-3, PARP and surviving
Goniothalamin	Increase death receptor DR5, decrease cFLIP, cleavage of PARP, caspase-3, caspase-8, caspase-9, Bid, Bax and Bcl2
Procyanidins	Activate caspase-8
Oplopantriol A	Up regulate TNFRSF10A, TNF, TNFSF8, CRADD, FADD, TRADD, caspase-3, -7 and -8
Maslinic Acid	Activate caspase-3 and caspase-8
Calotroposid A	Increase caspase-8
Propolis cinnamic acid derivatives	Regulate TRAIL/DR4/5 and/or FasL/Fas death-signaling loops and increase miR-143
Mertensene	Activate caspase-3 and PARP cleavage and increase TRADD
2-(Pro-1-ynyl)-5-(5,6-dihydroxypenta-1,3diynyl) Thiophene	ROS-Mediated JNK Activation
Riccardin D	Upregulate cleaved caspase-3, -9 and the ratio of Bax/Bcl-2, block the NF-κB signaling pathway
Icariin	Suppress the NF-κB activity
Oxymatrine	Activate PI3K/AKT/mTOR pathway

identified as a major feature of carcinoma cells; malignant colon cells prefer glucose to butyrate as their preferred energy source. As a result, malignant colon cells collect a lot of butyrate, which is an inhibitor of HDAC (Eslami et al., 2019). Butyrate can directly reach the nucleus, inhibiting histone deacetylase 1 and lowering short-chain acyl CoA dehydrogenase (SCAD) levels, which is the key step in mitochondrial butyrate oxidation catalysis (M Astbury et al., 2012). This inhibits CRC growth by reducing butyrate auto-oxidation in CRC cells (Han et al., 2018) and allowing butyrate to accumulate in carcinoma cells. This explains why tumour cells are more sensitive to HDAC inhibitors than non-transformed cells (Dashwood et al., 2003).

Table 5. Natural products regulating autophagy on colorectal cancer cells

Compound	Mechanism
Thymoquinone	Activate JNK and P38 and MOMP
Peiminine	Repress the phosphorylation of Mtor
Tanshinones	Induce LC3B-IIaccumulation
Epigallocatechin gallate	Induce LC3-IIaccumulation
Cardamonin	Increase p53/JNK
Isothiocyanates	Decrease the phosphorylation of Akt and mTOR
Salvianolic Acid B	Suppress Akt/mTOR pathway

7.2. Ursodeoxycholic Acid (UDCA)

Ursodeoxycholic acid (UDCA) suppress CRC by modulating inflammatory response and enhancing immune surveillance. Bile acids (BAs) are cholesterol-derived bile acids that are carried into the intestine by bile and help the intestine absorb fat. The 'traditional' mechanism produces two major BAs in the human liver: cholic acid (CA) and chenodeoxycholic acid (CDCA) (Dawson & Karpen, 2015). More than 90% of intestinal BAs are reabsorbed in the ileum and subsequently transferred to the liver via the portal vein, where hepatocytes digest them and secrete them back into the bile (Lin & Kohli, 2018). Unabsorbed BAs are converted into hydrophobic secondary bile salts by bacteria in the gut, such as Clostridium, Enterococcus, Bifidobacterium, and Lactobacillus. Gut bacteria, for example, convert CA to deoxycholic acid (DCA) and CDCA to lithocholic acid (LCA) (de Buy Wenniger & Beuers, 2010; Molinero et al., 2019; Ferrell et al., 2019). Clostridium species, including Clostridium absonum and Clostridium baratii, produce UDCA, which is a secondary bile acid. It shares a molecular structure with DCA, however unlike the hydrophobic bile acid DCA, UDCA has been shown to reduce the risk of colon cancer (Khare et al., 2008; Im & Martinez, 2004). Patients with colorectal adenoma who have been using UDCA for a long time are less likely to recur after the adenoma has been removed, and colonic

Table 6. Basic information for marine-derived anti-colorectal cancer natural products

Natural products	Marine organisms	Chemical class	Mechanism	Celltype/cell lines
Calothrixins	*Calothrix sp.*	Quinonoid	Anti- proliferation	HCT116
Salternamide A	*Streptomyces sp.*	Alkaloid	Cell cycle arrest	HCT116
6-bromoisatin	*Dicathais orbita*	Isatin	Apoptosis, Anti- proliferation	HT-29
Peridinin	*Gonyaulax polyedra*	Carotenoid	Apoptosis, Cell cycle arrest	DLD-1
Sipholenone A	*Siphonochalina sp.*	Triterpenoid	Cell cycle arrest	CaCo-2, HT-29
Sipholenol A	*Siphonochalina sp.*	Triterpenoid	Anti-proliferation, cell cycle arrest	CaCo-2, HT-29
Sipholenol L	*Siphonochalina sp.*	Triterpenoid	Anti-proliferation, cell cycle arrest	HT-29
Physcion	*Penicillium janthinellum*	Anthraquinone	Apoptosis	HCT116
Caldoramide	*Caldora penicillata*	Pentapeptide	Unknown	HCT116
Manzamine A	*Acanthostrongylophora sp.*	Alkaloid	Apoptosis	HCT116

epithelial proliferation is greatly reduced (Serfaty et al., 2003). The recurrence rate of atypical adenoma can also be reduced greatly with UDCA (Alberts et al., 2005). UDCA inhibits CRC in numerous ways, including increasing the hydrophilicity of the bile pool, lowering the concentration of hydrophobic BA (Ridlon & Bajaj, 2015), and regulating oxidative stress in colon cancer cells and CSC (Kim et al., 2017).

Furthermore, UDCA increases colonic MHC expression, which improves tumour immune surveillance (Rigas et al., 1994), reduces cox-2 in CRC, and inhibits NF-kappaB (NF-B) activated IL-1, as well as deoxycholic acid-induced A and AP-1 in human CRC cells (Shah et al., 2006). However, several researches have revealed that UDCA has little effect on CRC prevention (Pearson et al., 2019). Furthermore, high dosages of oral UDCA have been associated to an increased risk of CRC (Eaton et al., 2011). The effects of UDCA on CRC is still debatable, and more research is needed to verify its effectiveness.

7.3. Niacin

Niacin inhibits colonic inflammation and carcinogenesis via acting on G protein-coupled receptors (GRA) and prostaglandin receptors. Vitamin B is created by the intestinal microbiota, such as Lactobacillus acidophilus, in addition to being absorbed from the diet. Niacin, also known as nicotinic acid or vitamin B3, is a coenzyme precursor that includes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) and is required for cell viability (Peterson et al., 2020). Niacin is thought to have anti-inflammatory properties in addition to its hypolipidemic actions (Zeman et al., 2016). Niacin activates GPR109a, which improves the anti-inflammatory actions of colonic macrophages and dendritic cells, allowing them to differentiate into Treg cells and IL-10-producing T cells. Animal studies suggest that niacin can protect mice against colitis and colon cancer by activating GPR109a, albeit the exact molecular mechanism is unknown (Singh, N et al., 2014). Some studies have shown that niacin protects the intestinal mucosa by lowering TNF- levels via GPR109a (Salem & Wadie, 2017), while others have proposed that niacin protects the intestinal mucosa by mediating the release of prostaglandin D2 via GPR109a (Li et al., 2017). CSCs have a role in tumour development and maintenance; they are chemically resistant and have self-replenishing, multipotency, adaptability, and diversification properties. The removal of CSC could improve patient survival rates (Kharkar, 2017).

Niacin has also been demonstrated to have effects on tumour stem cells, with low dosages encouraging cell proliferation and large doses causing cell death in colon CSCs (Sen et al., 2017). However, no research into the mechanism of this phenomenon has been done so far. There are still many questions about whether niacin can prevent CRC and how it protects the intestinal mucosa from inflammation and CRC.

8. CONCLUSION

Natural products have been proven to have undeniable benefits and could be used to treat cancer. We highlighted the recently investigated natural items that have been employed or show significant promise for use in the treatment of CRC. The most serious issues with CRC treatment are drug resistance and side effects. Some natural products have been used with traditional chemotherapeutic medicines, such as 5-FU, to increase the cancer cells' susceptibility to conventional therapy, so enhancing the combined impact; this is a novel treatment technique for CRC. However, as more natural products are discovered, isolating novel active chemicals based on the finding of traditional natural products from terrestrial animals, plants, or microorganisms has become increasingly difficult. For example, a rising number of

known natural products are being identified regularly, obstructing the discovery of novel substances. As a result, finding new structural compounds is still a huge task.

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Chapter 7
Natural Products Possess Bioactive Agents Investigated for Their Anticancer Potential:
Medicinal Importance of Natural Products

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ABSTRACT

Cancer is regarded as a deadly disease and characterized as one of largest problems among the universal population. Worldwide, the population insists on a positive approach for curing the disease. However, plant resources are found to possess multiple phytochemicals which revealed promising effects for various cancer maladies. Over 60% of drugs are obtained from natural source only. Therapy for common cancer involves radiotherapy or chemotherapy, which alters the physical condition of the individual with diverse side effects and ultimately drains the immunity of the individual. Several available drugs are also unable to cure cancer completely, but recent advancement in utilization of plant-based compounds revealed greater beneficial efficacy in management of cancerous cell growth. Therefore, this chapter portrays the bioactive compounds obtained from natural sources and how these traditional medicines act as drug candidates against cancer.

1. INTRODUCTION

Natural products obtained from diverse plant resources have contributed a dominant function in therapy for various maladies. Among them, cancer is in second place and regarded as the most deadliest devastating malady in both developing as well as developed countries. (Lin et al., 2019; Siegel et al., 2020).

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Due to acceptance of insalubrious lifestyles such as drinking alcohol, smoking eating junk foods with high calorific value, no proper sleep at time, lack of exercise all connected with triggering the incidence of cancer (Jemal et al., 2011). The fundamental cause for increasing deaths around the world which is predictable to be approximately twenty one million by 2030 is none other than cancer (American Cancer Society 2016 and Siegel et al., 2020). (Shown in Table-1)

Among the 100,000 populace in India, the cancer occurrence rate were measured based on their annual average rate (AAR) in males and females (NCRP-ICMR 2013). The cumulative risk is among 0-75 age group. However, population based incidence of cancer globally as well as in India collected either from GLOBOCAN statistics/American cancer society provides us a distinct vision on increased rates of mortality. We have provided a broad overview global rate of cancer incidence rate which is regarded as contemporary burden and further also revealed the statistics of cancer in India alone in (graph 1)

Nonetheless, proliferation of cells in uncontrolled manner results in genetic instabilities and variations inside tissues, cells which transform normal cells to malignant cells. Although, several drugs are available for treatment for different types of cancers such as vinblastine (lymphoma, bladder), methotrexate (breast, bladder, cervix carcinoma), cisplastin, cyclophoshamide, paclitaxel, vincristine (ovarian carcinoma), doxorubicin (lung cancer) etc. Administrations of drugs for prolong duration leads to other side effects. Although, plants possess several bioactive agents which is regarded as gift of nature and helps to cure various ailments including cancer. However, several literature reports have depicted the medicinal importance of plant products (Aung 2017 and Tariq 2017). In our article, primary focus is on plant products which has rich bioactive phyto-constituents such as alkaloids, terpenes, flavonoids, lignans, taxanes, vitamins, minerals along with other primary as well as secondary metabolites. Nevertheless, we also displayed the molecular mechanism of action in inactivation of oncogenes, tumor suppressor genes. However, further docking studies would help researcher to study the protein-ligand interactions in order to combat the deadly disease.

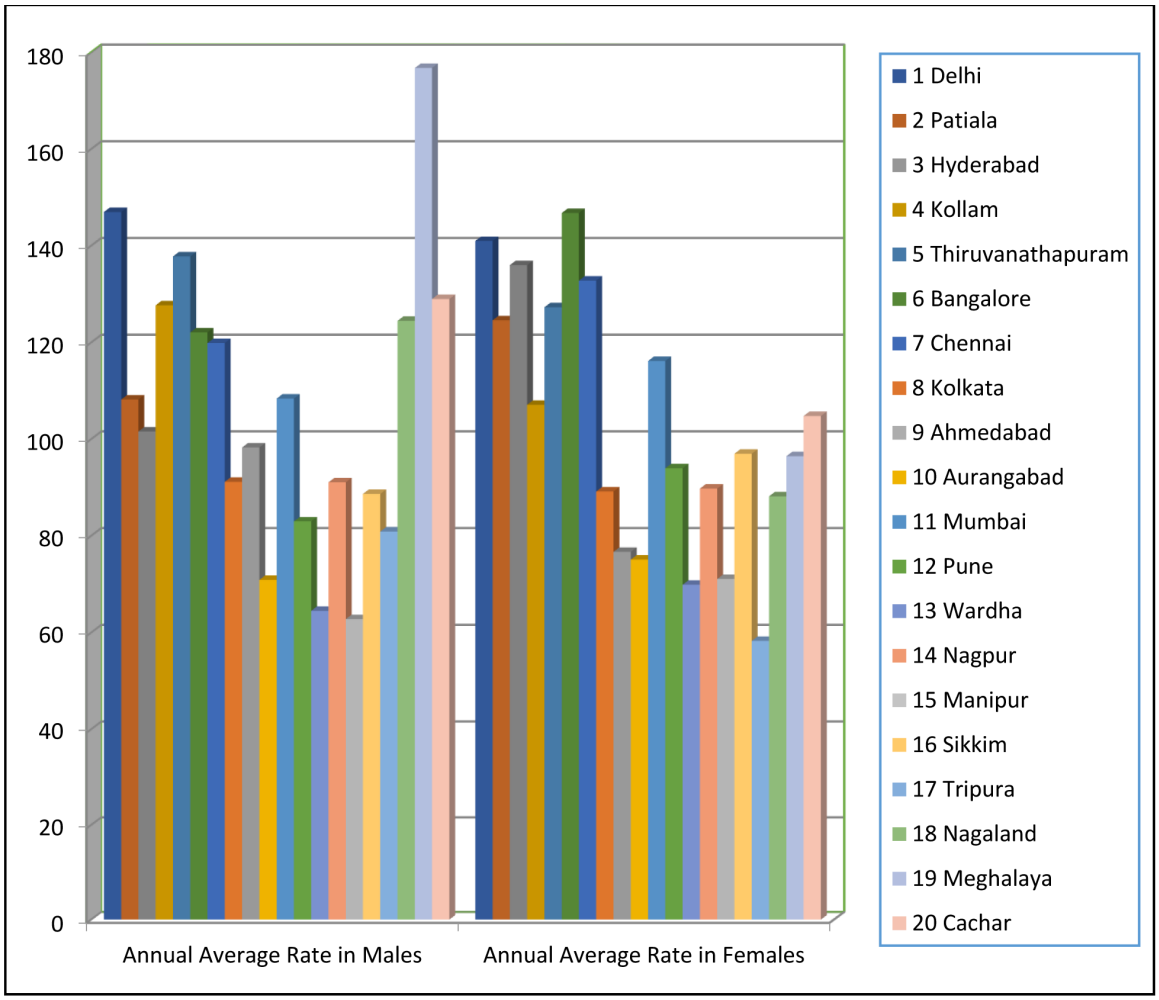
2. BIOLOGICAL SCREENING FOR PLANT DERIVED SUBSTANCES

Medicinal plants are nature's gift which possesses several bioactive compounds established as an inexhaustible resource for the production of new effectual drugs, pharmacophores and chemotypes (Veeresham 2012). Today usage of herbs for therapeutic purpose has spread universally (Koparde 2020). From decades, natural plants with medicinal importance have been depicted to show significant role in therapy and inhibition of various pathogenic diseases (Yuan 2016). Furthermore, herbal plants like Digitalis purpurea, Digitalis lanata, Camptotheca acuminata Decne., Artemisia annua L., Gingko biloba L., Curcuma longa L., Podophyllum peltatum L., Papaver somniferum L., Taxus brevifolia, Taxus baccata, Combretum caffrum, Euphorbia peplus, etc. From micro algae resources Spirulina platensis, cyanobacterial strain Lyngbya boulloni, Nostoc, Nodularia, and Anabaena (Voraˇcova, 2017). Marine macroalage, Chlorella vulgaris and Chlorella ellipsoidea (Cha 2008) are revealed to possess abundant bioactive constituents which are utilized for treatment of various ailments. Discovery of plant, marine and other related bioactive compounds at present utilized as pharmaceutical agents, remarkably used for therapy of cancer (Cragg 2016). (Shown in Figure 1)

Table 1. Estimated New Cases and Deaths for all cancers (GLOBOCAN Statistics 2020)

Site of Cancer	Estimated New Cases	Percentage in all sites	Estimated deaths	Percentage in all sites
Lung	2,206,771	11.4	1,796,144	18.0
Colon	1,148,515	6.0	576,858	5.8
Female breast	1,261,419	11.7	684,996	6.9
Non melanoma of skin	1,198,073	6.2	63,731	0.6
Liver	905,677	4.7	830,180	8.3
Rectum	732,210	3.8	339,022	3.4
Prostate	1,414,259	7.3	375,304	3.8
Stomach	1,089,103	5.6	768,793	7.7
Vagina	17,908	0.1	7995	0.1
Mesothelioma	30,870	0.2	26,278	0.3
Kaposi Sarcoma	34,270	0.2	15,086	0.2
Testis	74,458	0.4	9334	0.1
Hodgkin Lymphoma	83,087	0.4	23,376	0.2
Anus	50,865	0.3	19,293	0.2
Vulva	45,240	0.2	17,427	0.2
Gall bladder	115,949	0.6	84,695	0.9
Brain, Nervous System	308,102	1.6	251,329	2.5
Multiple Myeloma	176,404	0.9	117,077	1.2
Nasopharynx	133,354	0.7	80,008	0.8
Oropharynx	98,412	0.5	48,143	0.5
Salivary glands	53,583	0.3	22,778	0.2
Hypopharynx	84,254	0.4	38,599	0.4
Pancreas	495,773	2.6	466,003	4.7
Leukemia	474,519	2.5	311,594	2.5
Esophagus	604,100	3.1	544,076	5.5
Thyroid	586,202	3.0	43,646	0.4
Bladder	573,278	3.0	212,536	2.1
Cervix uteri	604,127	3.1	341,831	3.4
Lip, Oral cavity	377,713	2.0	177,757	1.8
Penis	36,068	0.2	13,211	0.1
Ovary	313,959	1.6	207,252	2.1
Melanoma of Skin	324,635	1.7	57,043	0.6
Corpus Uteri	417,367	2.2	97,370	1.0
All sites total	16,070,527		8,668,765	

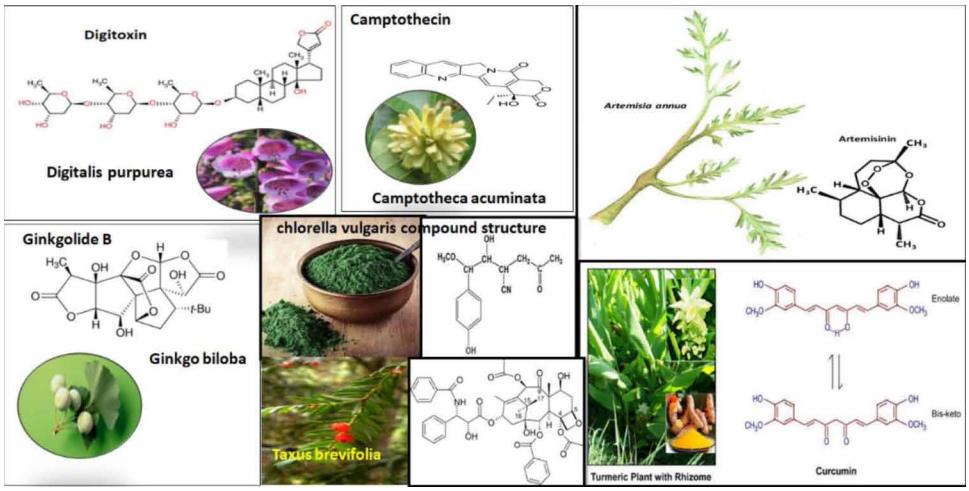
Figure 1.



3. PROMISING POTENTIAL OF PLANT DERIVED BIOACTIVE AGENTS

Ever since primordial decades the importance of medicinal plants have been acknowledged and consumed to improve health. These plant based products are the main resource for preparation of medicines for several maladies (Sakarkar *et al.,* 2011). Traditional plants possess secondary metabolites which possess bioactive compounds such as alkaloids, terpenoids, and phenolics (Kabera *et al.,* 2014; Delgoda and Murray, 2017). However, isolation of bioactive compounds from plant species is been carried out every year in order to exploit latest cytotoxic secondary metabolites which has the potential to combat against cancer. Medicinal plant products derived from plant sources have been examined to possess enormous promising bioactive phytochemicals from ancient times. (Samuelsson, 2004; Chin et al.,2006). However, many plant derived compounds have been legitimately subscribed for medicinal therapy (Balunas and Kinghorn, 2005). The list of some important plant derived compounds having significant medicinal value is depicted in Table 2.

Figure 2. Plant derived compounds with bioactive substances for cancer treatment



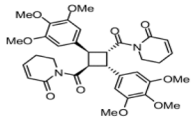
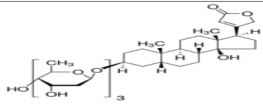
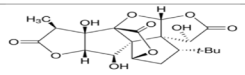
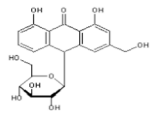
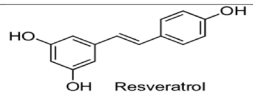
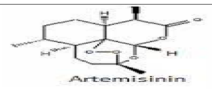
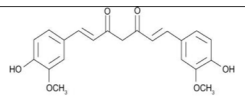
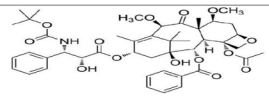
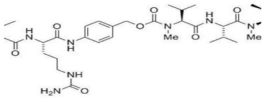
4. NATURAL PRODUCTS WITH PHARMACOLOGICAL INTERVENTIONS

The bioactive compounds obtained from plant sources either from, fruit, leaves, vegetables acts as potential chemopreventive agents against the deadly disease like cancer (Gullett et al., 2010). These compounds have the capability to intrude the biomolecules by either inhibiting, or reversing the tumorigenesis process (Cragg 2016) and thereby refraining the threat of recurrence of cancer (Pan et al., 2015). The unique ability of these compounds action is to impede carcinogenic agents, enhancing the aptitude of the DNA repair system or directly showing impact particularly against those cells that carry DNA alterations by mitigating speed of cell cycle or interrupting the proliferation of tumor cells to next stage of metastasis (de Melo 2018). These bioactive agents particularly targets on those early stages of transformation along with advanced stage of various cancer types (Kotecha 2016). However, the main constituents present in these plant sources are phyto-constituents which inhibit the progression of cancer either directly or indirectly. Furthermore, direct mode of action involves arrest of cell cycle, autophagocytosis and chromatin condensation. The indirect mechanism involves augmentation of phase II detoxification enzymes, transposing the unfavourable epigenetic regulations along with transforming expression of miRNA, altering the gut biota and proper balance of inflammation responses (Koh 2020). Thus, phytochemicals have greater contribution in assailing/ generation of oxidative stress which indirectly results in degradation of DNA. The antioxidant action helps in mitigation of cancer cell progression (Kiokias 2018). (Shown in Figure 23)

5. MECHANISM OF PHYTOCHEMICALS ACTIONS AGAINST CANCER

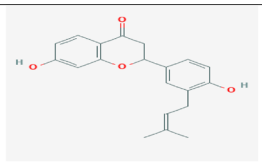
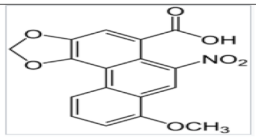
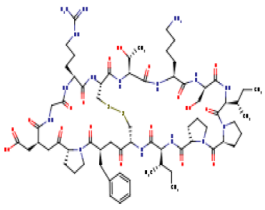
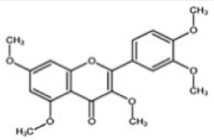
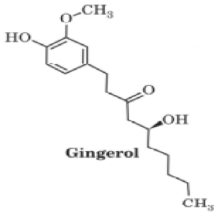
Plant based products such as fruits, spices, herbs and vegetables are rich in phytochemicals which support in health promotion and prevent diseases (González-Vallinas 2013). However, several literature reports have stated that consumption of fruits, vegetables and green leaves have shown beneficial impact in recovery from different types of cancer (Lee 2011). For instance, we have shown in (Table-3 and figure-4)

Table 2. List of plant derived bioactive compounds against different kinds of cancer

S. No	Medicinal Plant	Bioactive Compound	Structure of compound	Type of cancer	Outcomes	Reference
1	Piper longum	Amide alkaloids	Figure 2. 	Breast Cancer	Exhibited cytotoxicity against cancer cells Stress response to reactive oxygen species Induces apoptosis	Desai et al., (1988) Ee et al., (2010)
2	Digitalis purpurea	Cardiac glycosides are often termed digitalis or digitalis glycosides in particular digitoxin		Breast cancer	Instigated cell cycle arrest in G2/M phase via down regulation of cyclin B1 Induced DNA topoisomerases I and II and arrest of cell cycle	Goldin (1984) Manna et al., (2006)
3	Ginkgo biloba	Terpenoids		Breast cancer Ovarian cancer	Induces apoptosis Anti-inflammation Anti-angiogenesis	Itokawa et al., (1987) Kotakadi (2008)
4	Aloe vera	Aloin		Colon cancer	Decreases oxidative damage Inhibits inflammatory mediators (TNF-α, IL-6, iNOS)	Aoi (2011)
5	Vitis vinifera (Red grapes)	Resveratrol		Multiple myeloma Follicular lymphoma Breast cancer Colon cancer	Induce apoptosis Inhibit cell proliferation	Jang et al., (1997)
6	Artemisia annua	Artemisin		Cervical cancer Breast cancer	Induces apoptosis Increases cyclin B1 expression	Li (2007) Luo (2014)
7	Curcuma longa	Curcumin		Cervical cancer Pancreatic cancer	Curcumin administered along with cisplastin and radiotherapy helps in cancer therapy	Ranjan et al., (2013) Zhang (2016)
8	Taxus baccata	Cabazitaxel		Prostate cancer	Stops the growth of tumor cells from spreading and dividing	Heidenreich (2013)
9	Cyanobacteria: Symploca hydnoides and Lyngbya majuscula	Brentuximab vedotin 63 (Adcetris™)		Non-Hodgkin lymphoma and chronic lymphocytic leukemia	Has the ability to inhibit the tumor growth	De Goeij (2016)

continued on following page

Table 2. Continued

10	Brousson etia papyrifer a	2S-abyssinone II Verubulin		Glioblast oma; brain tumors	Arrest G2/M cell cycle Induces apoptosis	Grossmann (2012) Chamberlain (2014)
11	Allium wallichii	Steroids, terpenoids flavonoids, reducing sugars and glycosides	 **Quercetin** Figure 12.  **Kaempferol**	Prostate cancer, breast cancer, cervical cancer	Activates caspase 3 enzyme	Bhandari et al., (2017)
12	Aristoloc hia fontanesii	Aqueous extract		Breast, lung, ovary, prostate cancer	Significant tumor growth inhibition	Benarba and Meddah (2014)
13	Ipomoea batatas	Trypsin inhibitor protein		Promyel ocytic leukemia cells	Cx43 expression in several tumor cells as a trypsin–chymotrypsi n inhibition function, with antineoplast ic effects	Suzuki et al. (2005)
						
14	Citrus limon	5-hydroxy-6,7,8,30, 40 pentamethoxy-flavone		Human colon cancer	Inhibits proliferation of cancer cells	Hirata et al. (2009)
15	Zingiber officinale	6-Shogaol, Gingerol	 **Gingerol**	Ovarian and breast cancer	NF-kB nuclear translocatio n and IkBa phosphoryla tion via suppressing the expression of down-regulated iNOS and TNF-alpha	Ghasemzadeh et al., (2015) Oyagbemi et al., (2010); Meng

continued on following page

Table 2. Continued

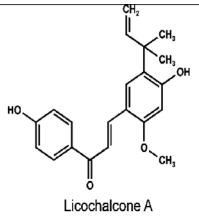
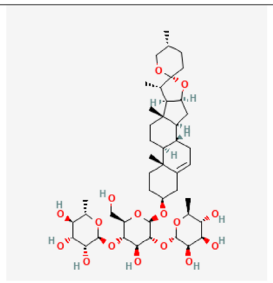
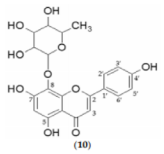
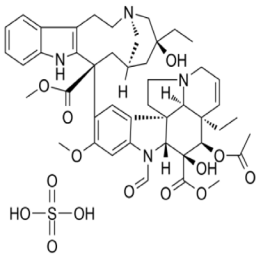
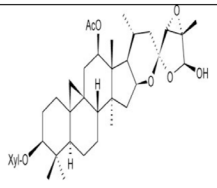
16	Glycyrrhiza glabra	Licochalcone-A	 Licochalcone A	Prostate cancer, breast cancer, Lung cancer, stomach cancer and kidney cancer	inhibits hypoxia-inducible factor-1α accumulation by suppressing mitochondrial respiration in hypoxic cancer cells	Zhang et al. (2016)
17	Dioscorea collettii	Dioscin		Liver and human gastric cancer	Cytotoxicity against human gastric carcinoma through death receptors and mitochondrial pathway	Hu et al. (2013)
18	Smilax chinensis	Tannin, saponins and flavonoids	 (10)	Sarcoma -180	Inhibits tumor cell proliferation	Madhuri and Pandey ascites sa
19	Catharanthus roseus	Vinblastine, vincristine		Breast cancer,Ovary cancer, Lung cancer, testis cancer	Interaction with tubulins and disrupts the assembly of the mitotic spindle, which in turn leads to the termination of actively-dividing cells.	Keglevich et al. (2012) Wang et al., 2016
20	Actaea racemosa	Actein		Liver cancer Breast cancer	Inhibits tumor cell proliferation	Einbond et al. (2009)

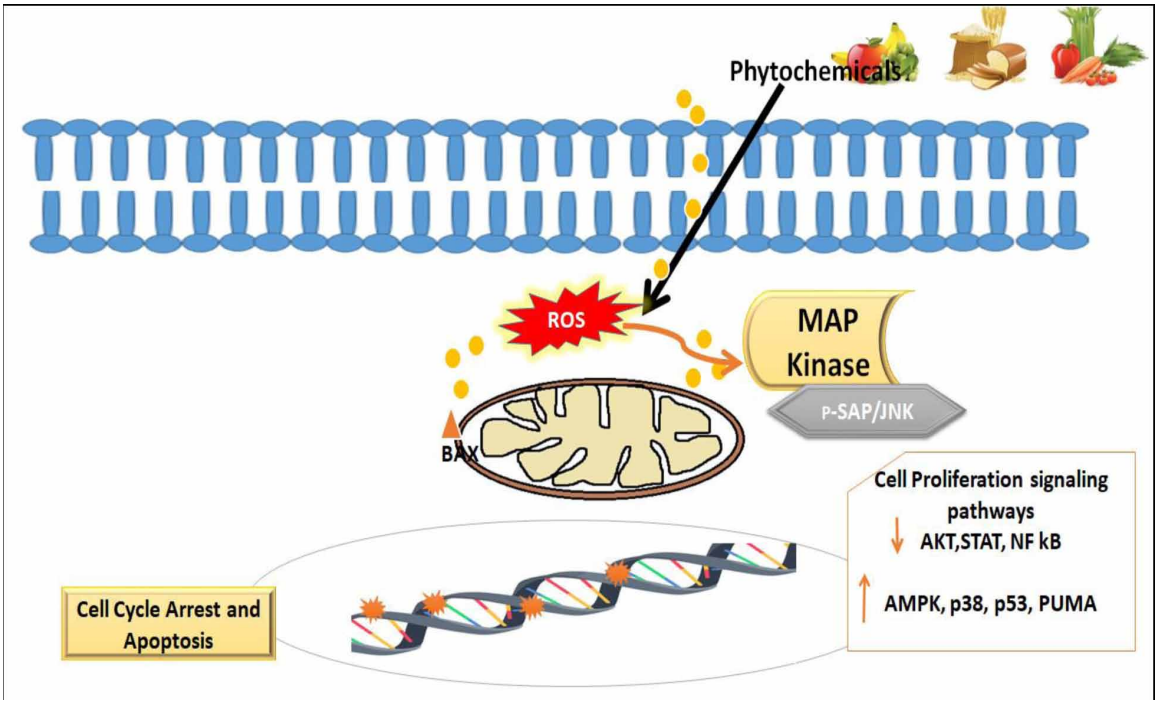
Table 3. Phytochemicals from plant products triggered ROS mechanism and arrest of cell cycle

Bioactive agents	Plant products	Investigated in In-vitro cells	References
p-Methoxycinnamic acid	Turmeric, rice bran, brown rice	HCT-116	Gunasekaran et al., 2015
Piperine	Piper nigrum, Piper longum	HRT-18	Yaffe et al., 2013
Curcumin	Curcuma longa	HCT-16	Watson et al., 2010
Quercetin	Red wine, nuts, fruits and vegetables	HT-29	Raja et al., 2017
Apigenin	Parsley,onions, wheat sprouts, fruits and vegetables	HCT-15	Banerjee et al., 2015
Resveratrol	Red wine, Grapes, mulberries	COLO201	Miki et al., 2012
Artocarpin	Artocarpus heterophyllus	HT-29	Sun et al., 2017
Patulin	Pears, Mold, apple and peaches	HCT-116	Kwon et al., 2012

about various phytochemicals exerting chemopreventive effects through triggering reactive oxygen species (ROS) mechanism which in turn induced cell damage along with cell cycle arrest and apoptosis (Fung 2010). These phyto-constituents are rich in bioactive compounds such as alkaloids, flavonoids, stilbenes (resveratrol), tannins, phenolics and cumarins (Tailor et al., 2012).

However, secondary metabolites obtained from the plant products are rich in bioactive compounds and connected with alteration in cell cycle. Furthermore, these phytoconstituents inhibits growth of cells at several check points. Nevertheless, activates receptor mediated as well as apoptotic signalling

Figure 3. Phytochemicals mediated redox sensitive mechanism resulting in cancerous cell cycle arrest



pathways which instigated reactive oxygen species and thereby activating cascade of caspases which ultimately resulted in death of cancer cells.

6. CONCLUSION

Our current article provided awareness as well as broad insights on the anticancer actions of herbal plants with greater medicinal values. From ancient decades, medicinal plants served as significant resources for the treatment of diverse kinds of disorders and diseases, including various types of cancer. These medicinal plants have bioactive compounds and with help of recent advancements in technologies assist against various cancer diseases. However, several literature reports have demonstrated the efficacy of herbal plants in curation of various ailments in their preclinical studies. Thus, further research need to be exerted on naturally active substances and study the protein-ligand interactions with computer aided drug designing. Later, in vivo trials on experimental models help us to study the pharmacokinetic and pharmcodynamic actions. Hence, natural compound have abundant medicinal importance and prove to be effective drug against various maladies including cancer. However, it is considered that plant compounds possess manifold phytochemicals which might exert potential effects on contrast to the same phytoconstituent taken separately. Thus, co-amalgamation anticancer phytoconstituents can even provide us more effectual therapeutic agents for cancer.

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Contributions

KRP and KRD contributed in writing, drawing figures and tables in this review article. KRP solely drafted this article. Rest all authors supported me and encouraged me.

Compliance with Ethics Requirements

NIL

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Chapter 8
Natural Products That Target Cancer Stem Cells

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ABSTRACT

The occurrence of tumor cells is generally governed by the cluster of cells known as cancer stem cells, which are based on the informative model of cancer tissue consisting of stem cells that do have characteristics like auto-renewal activity and also provide intrinsic mechanisms for survival which are responsible for resistance against tumor cells to most of the drugs used in chemotherapy to cure cancer. During the course of therapy, it is difficult to eliminate CSCs due to which recurrence of tumor and metastasis develops inside the cell. Ongoing studies provide significant information on the particular phenotypic characteristics of cancer stem cells from different tumor types, as well as the signaling system and molecules that undergo auto-renewal and drug resistance. NPs (natural products), which are derivative of botanicals and food sources, may alter important signalling pathways that are involved in the perpetuation of CSC phenotypic traits. The chapter deals with the use of plant products to cure CSCs and their functioning.

INTRODUCTION

In recent year's various diagnostic and treatment technologies like radiotherapy, antineoplastic and chemotherapeutic drugs not only have made many solid tumors cure possible but also have given a new ray of hope to those people who are diagnosed with cancer. Although in numerous cases of cancer patients, the prognosis remains bleak because of the MDR (multiple drug resistance) and the high cancer recur-

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rence rate visualized after the initial treatments of chemotherapy. Specifically, the cancers that affect patient multiple organ systems, i.e., metastatic cancer, are very difficult to treat, and sometimes complete or partial surgical resection of patients multiple tissues is required. Possibly CSCs (cancer stem cells) will explain the shortcomings that exist in the established treatments like chemotherapy. Usually, these cancer stem cells are the small tumor cells population having the ability to form phenotypically diverse tumors, which can differentiate and self-renew (Ahmed et al., 2013).

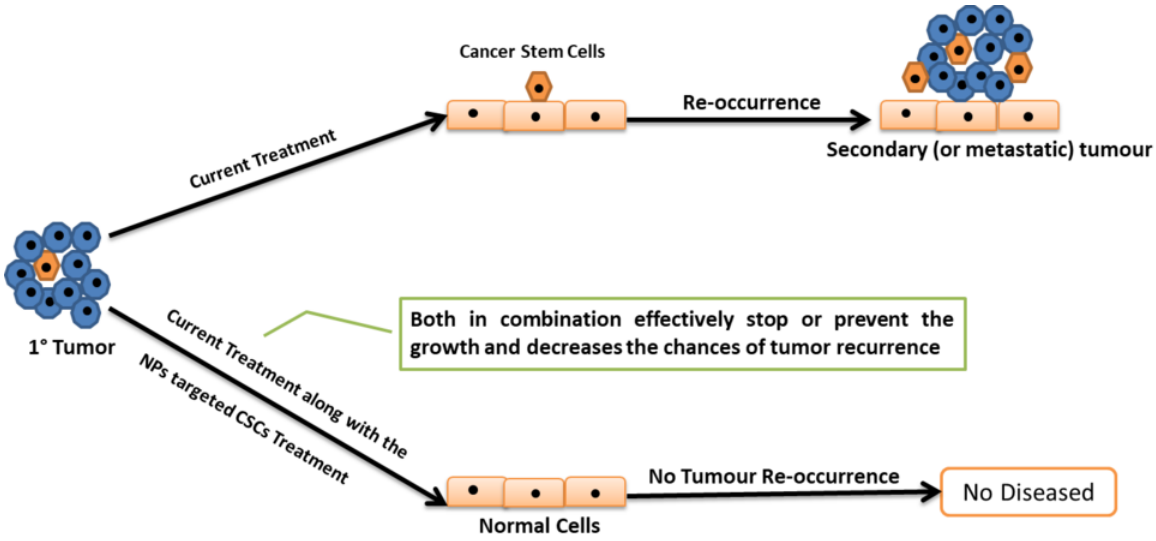
CSCs are described as the TICs (tumor-initiating cells) group that might have stem cell-like features. However, it is not very much clear whether the tumor cell's plasticity allows other cells to turn into the stem cell and attain the ability to restate heterogeneous tumors. In the late 90s, it was Bonnet and Dick who first identified the CSCs' role in tumor formation (Bonnet and Dick, 1997). In their research studies, they have revealed that the subpopulation of $CD34^{+}/CD38^{-}$ cells (from acute myeloid leukemia) forms tumors in immunodeficient NOD (nonobese diabetic)/SCID (severe combined immunodeficiency) mice with greater effectiveness than the subpopulation of $CD38^{-}/CD34^{+}$ cells. Because of the ability of cancer stem cells to divide unequally allows them to differentiate and self-renew to produce dissimilar tumors that contain multiple phenotypes were also recognized. After this research, the cancer stem cells hypothesis was carefully verified. The results suggest that these cancer stem cells play a vital role in the growth of tumors for various cancers (Marchand and Pinho, 2021). Which includes colorectal carcinoma (O'Brien et al., 2007), hepatocellular carcinoma (Suetsugu et al., 2006), breast carcinoma (Liu et al., 2021), neck squamous cell carcinoma (Picon and Guddati, 2021), lung carcinoma (Paterson et al., 2021), pancreatic carcinoma (Li et al., 2009), glioblastoma (Patrawala et al., 2005), and ovarian adenocarcinoma (Szotek et l., 2006) are among the others. According to the CSC (cancer stem cells) hypothesis model, the recurrence of cancer after the treatment is because of the higher CSCs resistance towards the cellular toxins. Whereas the current treatments have the ability to successfully remove the bulk portion of the tumor mass, but due to its ability, the remaining CSCs form fully developed new tumors from the few left cells or even from the one left cell.

These cancer stem cells are thought to show resistance to different treatments via a number of cellular mechanisms like the detoxifying enzymes, quiescence, and drug efflux pumps (Zhang et al., 2017). According to the reports, the higher CSCs population within the tumor was found subsequently linked to MDR (multiple drug resistance) and poor diagnosis for cancer suffering individuals (Lee et al., 2011). CSCs are assumed to start the development of metastatic tumors by undergoing epithelial-mesenchymal transition, migrating to different organs, and finally reattaching by MET.

Various currently used methods for cancer treatments have been found unsatisfactory in abolishing the cancer stem cell populations from many types of cancer. A $CD133^{+}$ glioma (a tumor type that occurs in the spinal cord and brain) CSCs were found to show a higher degree of resistance to radiation therapy than their counterparts $CD133^{-}$ (Bao et al., 2006). In a similar way, the resistance was shown by breast cancer stem cells also to radiotherapy treatments (Li et al., 2008). Likewise, in residual breast cancer tumors, the CSC population was found to significantly increase after chemotherapy treatments, almost doubling the residual cancer cells tumorigenic potential in immunodeficient SCID (severe combined immunodeficiency) mice (Li et al., 2008).

Generally, a treatment that targets the specific surface markers or molecules is expected to fail in eliminating the CSCs, because of the many activated survival pathways in cancer stem cells along with the cancer stem cells markers uncertainty across the various organ tissue types. Thus various treatments that are capable of decreasing the populations of CSC will need the development of new multi-targeted, diverse, and novel methodologies for the treatment of cancer patients. But still, due to the various, poorly

Figure 1.



understood CSCs characteristics, the finding of therapies targeting the CSC will possibly be the outcome of opportunistic screening of known or new compounds against the populations of CSC.

Therefore natural products can play a crucial role in discovering the novel treatments needed due to the difficulty of treating the CSCs. NPs (natural products) are rich sources of active compounds; that's why they are very important for the pharmaceutical industry. NPs value in medicine because of their capability to affect various signaling pathways simultaneously and produces minimal or negligible side or toxic effects. Because of the success of these natural compounds, particularly in the area of cancer treatments, has attracted scientists to examine the effect of various natural products on cancer stem cells. Figure 1 briefly describes how natural products (NPs) can be utilized in targeting cancer stem cells (CSCs). In this book chapter, a brief description of some selected NPs that have the ability to target CSCs is provided.

CSCS THERAPEUTIC IMPLICATIONS IN TREATING CANCER

The main factor that may contribute to the recurrence of tumors is because of the failure to assess the response of CSC in cancer patients receiving the chemotherapeutic drugs as recommended by many retrospective studies challenging the current RECIST guidelines for analyzing the clinical trial effectiveness of the cancer therapeutics (Eisenhauer ey al., 2009). Criteria like the tumor size, progression time, and progression-free survival for assessing the efficacy of therapeutic drugs will be challenged for not reflecting the patient result accurately. Because of it, this new guideline was proposed for assessing and standardizing the response criteria in well-established stem cell-related malignancies (Savona et al., 2015). To inactivate the cytotoxic drugs, CSCs have many intrinsic drug resistance mechanisms, which lead to the recurrence of the tumor (Scioli et al., 2021). Most chemotherapeutic drugs affect the differentiated tumor cell's apoptotic response, thus conferring the cancer stem cells with an existence advantage with even better proliferative potential (Zheng et al., 2010). Thus the tumor cells re-populate

with the lineage-dependent phenotypic and genotypic modifications, including MDR (multiple drug resistance), which make CT (chemotherapeutic) drugs ineffective, resulting in rapid progression of the disease and inferior prognoses (Yokoyama et al., 1999).

Moreover, the hypoxic stability of cancer stem cells supports them to survive even in the adverse microenvironments that even challenge the accessibility of drugs to that niche and result in MDR. Suppose cancer stem cell response is really a crucial criterion for evaluating cancer treatment. In that case, there are no therapeutic medications are available for clinical use which precisely targets the cancer stem cells. The main complication in developing the cancer stem cells specific drugs is CSCs genotypic variability as well as the genomic instability of HP (hyper-plastic progeny), which makes the karyotyping of tumor cells extremely challenging (Grichnik, 2006). But these CSC self-renewal programs can be effectively targeted by using natural products ahead of cell differentiation programs that hinder the growth of multiple drug resistance-associated mutations during the tumor development, which may lead to refractory reply to patient treatment (Angeloni et al., 2015). A natural product has shown favorable effects in alerting the cancer stem cells to chemotherapeutics by targeting the signaling pathways that control the cell's differentiation and self-renewal properties of cancer types (Nautiyal et al., 2011). Therefore, in combination with the chemotherapeutic drugs, these natural products can form a potent dual-target drug therapy against the tumor cells and CSCs.

DRUG RESISTANCE IN CSCS

Generally, it is not obligatory to define cancer stem cells with respect to chemotherapy treatments; resistance to the drug is correlated with cancer stem cell populations. It has been observed that drug resistance is directly proportional to an increment in the number of cells retaining CSC markers (Li et al., 2021). Resistance to particular chemotherapeutic compounds involved in cancer cell lines is usually raised by exposure of cells to constantly high doses of a specific drug or by subjecting them to repeated cycles of clinically admissible dosage, which is generally followed by media free from the drug that imitates the treatment which is received by patients (Li et al., 2021). The improvement of cancer stem cells following chemotherapy treatments observed in both clinical as well as *in vitro* studies has vast implications on the future treatment of cancer as well as on drug discovery. Without the targeted killing capacity of CSCs, patients will possibly face the problem of reappearance of tumors after chemotherapy. There is a number of properties and proteins that are thought to be involved in providing drug resistance against CSC and are therefore useful for ideal targets in future chemotherapy or chemo-drug discovery processes. It is normally observed that non-cancerous stem cells possess many properties that provide drug resistance to cancer stem cells, and further, it results in undesirable after-effects on healthy cells and tissues.

ABC TRANSPORTERS

ABC (ATP-binding cassette) transporters are a very crucial class of membrane-linked transporter that are actively involved in the protection of noncancerous stem cells in the entire human system. The significant role of these protein classes is to pump out harmful substances before their toxic effects cause' death of cells. These pumps are involved in the removal of diverse toxic compounds, including chemotherapeutic drugs. ABC transporters expression point out CSC phenotypes in various different tissues

and is also involved in the development of multiple drug resistance (MDR), specifically of cancer stem cells (Moitra, 2015). There are some members like ABCB5, ABCG2, and ABCB1 that belong to the family of ABC transporter, which seems to be vastly expressed in CSCs, but still, they are not limited to proteins. These proteins and their expressions act as a biochemical marker for cancer stem cells, but due to the absence of proper antibodies, its detection becomes impractical. While the ability of the side population to exclude the Hoescht 33342 (a fluorescent stain) is due to the ABC transporters (more precisely ABCG2) making isolation of side population as an indirect procedure of cancer stem cell culture supported by expression of ABC transporter (Moitra et al., 2011).

The discovery of different types of ABC transporter proteins multiple times in relation to chemotherapy resistance leads to confusion in classifying them. For example, proteins that resist breast cancer include transporter ABCG2 because of its ability to confer MDR against breast tumor cells. Many cancer models, which include K-562 myeloid leukemia and adenocarcinoma MCF7 breast cells, express ABCG2 protein, which provides drug resistance to the affected cells (Nakanishi et al., 2006). The cell lines were subjected to chemotherapies, and the selection of resistance cell lines was made based on the experiment that included various drugs. ABCB1 is also designated by other names like multidrug resistance protein 1, P-glycoprotein 1, and CD243. ABCB1 is useful for the influx of different types of chemotherapeutic compounds like *vinca* alkaloids, anthracyclines, and taxanes, making it a suitable multiple drug resistance protein. Reduced expression of ABCB1 protein increases chemotherapeutic sensitivity of colon-rectal cancer stem cells additionally to multiple drug resistance cell lines of different ancestry (Katayama et al., 2014). The processes by which ABC transporters can be targeted provide an alternative way of resistance against cancer cell lines and help in strengthening traditional methods of chemotherapy.

ALDH ENZYMES

Another mechanism that cancer stem cells utilize in order to possess multiple drug resistance is the rapid consumption of chemotherapeutic substances. It is already well reported that the activity of the ALDH enzyme act as a biochemical marker that is used to diagnose cancer stem cells. ALDH enzymes oxidize aldehyde groups of chemotherapeutic drugs, further helping in the metabolization and detoxification of cells. ALDH enzymes are significantly involved in the process of differentiation of normal and malignant cells. It was reported that there was a loss in multiple drug resistance when $ALDH^{hi}$ activity was inhibited in the case of breast cancer (Croker and Allan, 2012).

Further, by applying di-ethyl-amino-benzaldehyde ALDH activity was inhibited, which resulted in strengthening the response of cancer stem cells against radiation therapy. By inhibiting the enzyme activity of ALDH from tumor cells, the metabolization of chemotherapeutic substances within the affected cells occurs at a very slow rate that would be useful for proper treatment. Cellular toxic substances which are not considered as a substrate for ALDH enzymes or decrease their enzyme activity may be useful in inducing apoptosis in cancer stem cells and can provide a ray of hope for future treatment (Croker and Allan, 2012).

PRO-SURVIVAL SIGNALING AND STEM CELL MAINTENANCE

Cancer Stem Cells seize pro-survival signaling mechanisms and proteins responsible for the maintenance of normal stem cells. In a similar manner, cancer stem cells have the ability to resist cellular stress and destroy differentiated cancerous cells. It is reported that targets induced by rapamycin and activator of transcription 3 and signal transducer help in the proliferation and maintenance of normal and cancerous cells. While the activation process of PTEN and successive inhibition of STAT3 and mTOR results in a rapid decline in cancer stem cell viability and drug resistance against tumor cells (Zhou et al., 2007).

It is reported that various stem cell proteins that are responsible for maintaining healthy cells are also up-regulated stem cells. These groups of proteins include Wnt, Hedgehog, and Notch. These proteins are involved in the maintenance of stem cell-like activity of cancer stem cells and trigger the expression of different transcription factors associated with stem cells, for example, Oct4 and Nanog factors (Cochrane et al., 2015). Maintenance proteins of cancer stem cells are involved in the asymmetric division, further allowing them to endure severe stress conditions. Dysfunctioning of these pathways leads to facilitating progressive cancer stem cells differentiation responsible for reduced tumor viability against chemotherapeutic substances, providing an effective target to combat both types of tumors, so-called benign and malignant (Cochrane et al., 2015).

QUIESCENCE

Cell quiescence is generally referred to by attenuated mitotic divisions within the different populations of cells. Quiescence is a significant characteristic of healthy stem cells, which helps them to endure in a state of dormancy and is responsible for the reduction in DNA mutation rate for a longer period of time (Shen et al., 2021). While still there is a controversy about whether or not chemotherapeutic drugs have reduced effect on the dormant cell, an experiment performed to break the dormancy of these cancer stem cells resulted in higher sensitivity against chemotherapeutic agents (Borst, 2012). The process behind the MDR resistance is based on the assumption of declined metabolism related to cancerous cells, discontinuity of cell cycle, and absence of DNA replication hinder chemotherapeutic agents. Cancer stem cells that are under quiescent phase not only affect MDR but also allow the cells to maintain a dormant stage at the location of the injury or move across the human body for a longer period of time before adhering and starting the initiation of tumors. The process of targeting the quiescence phase of cancer stem cells will lead to the efficacious treatment of current therapeutic methods against CSCs (Borst, 2012).

NATURAL PRODUCTS AS CSC PATHWAYS MODULATORS

Modulation of the ABC Transporters

It has been reported that NPs is directly involved in activity assay related to cancer stem cell, or it has been proven that their activity targets the cancer stem cell renewal process. Various different types of phytochemicals such as carotenoids, lycopene, violaxanthin, capsanthin, capsorubin, lutein, antheraxanthin, and flavonoids and different traditional Chinese herbal medicine exhibit ABCB1 and ABCG2 modulating effect (Eichhorn and Efferth, 2012). The secondary metabolite allixin, which is purified from

garlic, exhibits anti-tumor promoting effects, preventing the process of development of skin tumor by activating tissue plasminogen activator in DMBA initiated mice. Numerous plant secondary metabolites such as polyphenol, triterpenes, and flavonoids, and several different phytochemicals were tested in membrane-based transport preventive assays of ABCG2. The non-flavonoid plant-based secondary metabolite such as berberine, limonin, ursolic acid, sinapic acid, and oleanolic acid displayed inhibition of the ABCG2 mediated pathway. Various other flavonoids such as laricitrin, quercitrin, chrysoeriol, myricetin, pinocembrin, tamarixetin, tricetin, and tricetin were also described as potent inhibitors of ABCG2 transporter (Tan et al., 2013).

Interestingly, tetrahydrocannabinol acts as a potent inhibitor of ABCG2 with an IC50 of 1.7μM concentration. The investigation related to the interaction between the ABCG2 transporter and different bisbenzylisoquinoline alkaloids was carried out (Tain et al., 2013). Using the BCRP model of cells, the researcher was able to describe that the alkaloids, basically liensinine and dauricine, act as a substrate for ABCG2, verifying their results by the technique of molecular docking. Based on accumulation of these substances and interaction with the substrate at ABCG2 may provide a cause for excretion of dauricine and liensinine. The antagonist activity of these substances against ABCG2 could be applicable in chemosensitizing cancer stem cells to the lethal effect of different CTs (Tain et al., 2013).

Iso-thiocyanates

Vegetables belonging to the Brassicaceae family, such as sprouts, Cauliflower, and broccoli, constitute iso-thiocyanates which include sulforaphane, that is hydrolyzed by enzymatic action from glucosinolates (Kaiser et al., 2021). Alteration in the phosphorylation process of different types of kinases, including their substrates such as JNK, GSK3, and PKC by dietary isothiocyanate and sulforaphane, was observed (Forster et al., 2014). Sulforaphane was also involved in the treatment of breast cancer cells and was linked with a decrement of AKT, β-catenin, and phospho-GSK3β (Li et al., 2010). Sulforaphane was reported to have potential chemopreventative properties, as observed in the case of cancers in animal cell models. It was observed that sulforaphane is responsible for abrogating the resistance of pancreatic cancer stem cells to TRAIL ligand by hampering with TRAIL-activated NF-κB signaling process (Kallifatidis et al., 2009). Hence, their study proved that a combination of TRAIL and sulforaphane would provide a possible strategy for the useful treatment of pancreatic cancer stem cells. Sulforaphane has also involved down-regulating NF-κB factor activity in colon and prostate cells suffering from cancer. It has been observed that there was suppression in gene expression of WNT-9a that occurred in ApcMin/+ mouse adenomas treated with sulforaphane (Khor et al., 2006).

Salinomycin

Salinomycin is an antibiotic extracted from the bacteria *Streptomyces albus* that has been effectively utilized to kill cancer stem cells in various forms of human cancer, mostly by disrupting the function of the ABC drug transporter WNT pathway and different types of cancer stem cell pathways. Till now, it is unclear that by which process salinomycin destroys cancer stem cells, but it was observed that salinomycin, in conjunction with other cytotoxic drugs, was much efficient in eliminating human cancer cells in mice xenograft than the cytotoxic drug alone (Kai et al., 2015). This technique supports the idea of efficient treatment of cancer by targeting different types of cell populations suffering from cancer, including cancer stem cells and progenitors, which are differentiated.

Polyphenols

Chemo preventative activity against different kinds of cancer was observed in extracts of green tea having a high content of polyphenolic catechins, which includes epigallocatechin-3-gallate (EGCG). It has been already proved that EGCG has inhibitory action against NF-κB activity, MAPK pathway, activator protein 1, and EGFR- singling with reduced expression, etc. (Miyata et al., 2018). Several approaches of EGCG are possibly associated with functional inhibition of WNT. EGCG is responsible for hampering WNT signaling by the process of stabilization mRNA of WNT inhibitor HMG-box transcription factor 1 (HBP1), resulting in reduced proliferation of cancer cells of the human breast (Kawasaki et al., 2008). Other researches prove that EGCG activates endogenous WNT protein, which acts as an inhibitor of SFRP1 in hepato-blastomas (Godeke et al., 2013). A transgenic model of EGCG-treated mice ApcMin/+ from which adenomas cells were isolated, which is known to be the best model for studying colon cancer in humans, showed repression in the genesis of tumors as proven by the nuclear movement of β-catenin, low level of pAKT l and decreased in size of adenoma affected tissues. EGCG was reported to be involved in hampering the chaperon activity of HSP 90 in pancreatic cancerous tissue, thereby reducing AKT signaling (Li et al., 2009). EGCG is supposed to regulate NF-κB activity in a negative course of action by hindering its ATP or IL1β activation process. Shh gene regulation and Hedgehog signaling system are being examined as potential targets of EGCG. However, a number of research prove the effectiveness of EGCG to especially modulate CSCs in different forms of cancer. (D'Angelo et al., 2014). Eid et al. studied the cellular toxicity of different plant metabolites, including phenolics compound (EGCG, thymol); terpenoids (menthol, aromadendrene, sitosterol, and carotenes), and alkaloids (glaucine, sanguinarine, and harmine) were examined alone or in conjugation with the cellular to toxic steroidal saponin digitonin in CEM/ ADR5000, Caco-2, CCRF-CEM, and MCF-7 cells. Digitonin, in conjunction with different metabolites like terpenoids, phenolic acid, and alkaloids and showed synergistic therapeutic activity in multiple drug resistance cells like CEM/ADR5000, expressing a higher level of ABCB1 proteins (Eid et al., 2012).

Isoflavones

In recent studies conducted by researchers, it was observed the intake of dietary soya iso-flavones like genistein had lowered the possibility of breast cancer in humans (Verheus et al., 2007). The soya isoflavonegenistein acts as a potent ant proliferative agent due to its chemical properties against different types of cancer. Isoflavones from soya were effective against the phosphorylation of AKT and FOXO3a, up-regulating GSK3β expression, which leads to advancement in phosphorylation reaction of βcatenin in cancerous cells of the prostate (Sarkar et al., 2009). It was reported that genistein reduces β-catenin mediated expression of WNT target genes in mammary epithelial tissue cells by increasing the expression level of E-cadherin (Su and Simmen, 2009). It was also observed that suppression of tumor formation in breast cancer cells of humans by the effect of soya iso-flavonegenistein and blueberry polyphenols exhibiting the possibility of diet-regulated targeting of cancer stem cells progenitor. Ning et al. examined genistein activity and observed specified action against ovarian cancer stem cells mediated low expression of FOXM1 (Ning et al., 2014).

Sulforaphane

It was reported that there was no expression of β-catenin in human cervical carcinoma HeLa and HepG2 cells, although it is still unclear whether there is a direct effect on cancer stem cells or not till now (Park et al., 2007). Sulforaphane has been demonstrated to hamper the expression of the AKT pathway in various different types of cancer that include different organs ovary, prostate, and colon-rectal cancers, and it was described that PI3K/AKT pathway helps in the regulation of breast cancer stem cells by advocating downstream process related to β-catenin through phosphorylation of GSK3β (Korkaya et al., 2009). A research carried out on NOD/SCID mouse cultured with tumor cells determined from sulforaphane treated xenografts showed no tumor re-growth up to thirty-three days. On the other hand, control tumor cells rapidly generated a large number of tumors (Li et al., 2010). This process was generally linked with a low expression level of WNT/β-catenin in the auto-renewal pathway due to sulforaphane-treated breast cancer tissue.

Vinca alkaloids

Vinorelbine, an important vinca alkaloid, is generally prescribed as an efficient metabolite for treating breast cancer cells (Liu et al., 2008). A patient suffering from colorectal carcinomas treated with vinorelbine its screen was obtained. However, when examined, remission of tumors and reoccurrence of cancer cells due to high proliferative rate and overexpression of cancer cell markers BM1, NANOG, CD44, DR5, and CD133. It was reported that mTOR signaling and Notch transmission pathway might cause these effects (Liu et al., 2008).

Curcumin

Curcumin is a secondary metabolite that has been examined for its anticancer activity. It is polyphenol generally extracted from turmeric, a spice that is broadly utilized in the Indian subcontinent and in different Middle-East Asian meals. Curcumin has been reported to have anti-inflammatory activity and enhance the death of cancerous tissue (Kakarala et al., 2010). It has been involved in different medical tests describing its effectiveness at higher concentrations and its effectiveness to counter pancreatic cancerous cells in individuals despite its least assimilability (Kakarala et al., 2010). The anti-tumor forming characteristics described by curcumin have led to the examination of potential targeted cancer stem cells.

Curcumin helps in inhibiting the genesis of breast cancer in vitro by fifty percent and hundred percent applying 5 micromoles and 10 micromoles concentrations, accordingly describing the capacity of curcumin to block Cancer cells' capability to go through EMT (Kakarala et al., 2010). A similar counterpart of curcumin, named GO-Y030, was involved in inducing programmed cell death, reducing tumorsphere production, and blocking STAT3 phosphorylation in Aldehyde dehydrogenase^{+}/ prominin-1 colon cancer stem cells when applied at 2 to 5 micromoles concentrations. The capability of this compound to attack tumor-forming cells was further shown by the use of the NOD/SCID mouse system. When GO-Y030 is provided in 50 mg kg^{-1} through retroperitoneal injection, the tumor size in xenograft implantation of 10^5 cancer stem cells was reduced by approximately fifty-eight percent (Lin et al., 2011). Curcumin also acts as a supplement to the presently persisting chemotherapy process. Curcumin can be further utilized when given in conjunction with FOLFOX, a frequently suggested mixture of leucovorin Ca^{+2}, fluoro-

uracil, and Eloxatin was effective in reducing the sustainability in EMT of colon cancer stem cells up to some degree as compared with FOLFOX (Li et al., 2021).

Although curcumin acts as a potent anticancer compound and has widely been applied in numerous medical tests against carcinoma, it has many defects that are similar to resveratrol. Specifically, the advanced metabolization and secretion of curcumin with its hydrophobic nature result in decreased biological availability, which has been further described by the mice system as a model (Pan et al., 1999). A number of drug delivery techniques have been applied to enhance the bio-availability of curcumin which include the application of adjuvants that interfere with metabolic activities, the process of encapsulating in liposomes, use of nanoparticles, and application of different suitable structural counterparts (Aggarwal and Sung, 2009).

Parthenolide

Parthenolide falls under the lactones category sesquiterpene of the class germacranolide, which is found in nature in very few plants (Tanacetum parthenium). The researchers examined the mode of action of parthenolide against cancer stem cells which were originated AML and CML (Guzman et al., 2007). Parthenolide triggered programmed cell death in blast crisis CML and acute myeloid leukemia cells while up to some extent in hematopoietic cells (Hellsten et al., 2011). While in NOD (nonobese diabetic)/SCID (severe combined immunodeficiency) mice, this showed exclusive targeting of stem cells and AML progenitor in comparison to different CT medication, cytarabine. Blockage of NF-κB (protein complex), a pro-apoptotic activator of gene p53, and also increased ROS were several factors responsible for parthenolide action against these cancer stem cells. Fungal compound, Galiellalactone, which can be extracted from the class of ascomycetes. A researcher has observed that galiellalactone blocks cancer stem cells such as $ALDH^+$ LNCaP and DU145 cancer cell proliferation process, and tumor removal in mouse xenografts occurs by targeting JAK-STAT (signaling pathway) phosphorylation of STAT3 (Hellsten et al., 2011).

Berberine

Berberine is a secondary metabolite (alkaloid) which is an isoform of quinoline that generally occurs in different parts of medicinal plants. Berberine has been used from ancient times in Ayurvedic medicine due to its anti-inflammatory properties, and this metabolite has been reported to induce a gradual process of apoptosis, initiated by ROS species production, in different types of carcinoma (Meeran et al., 2008). The process of programmed cell death initiated by berberine moves through an obligate pathway which is caspase-9 dependent and generally involved in hampering the integrity of the mitochondrial membrane. Unlike many other compounds, the usage rate of berberine is very less for the human body, restricting its potential application as a potent drug to treat various types of cancer. This limiting factor can be removed by liposomal mediated targeting as an advanced drug dispensing technique (Ma et al., 2013). This dispensing technique involves encapsulation of berberine compound into liposomes which are then used to deliver the substances exactly to the mitochondria of $CD44^+/CD24^-$ breast cancer cells. Further, by applying this technique, 1-50 micromoles of berberine compound potentially produce dose-dependent programmed cell death in breast cancer tissues. Further, the drug induced the expression of the pro-apoptotic factor Bax and triggered caspase 9 and 3, causing apoptosis in cancer stem cells isolated from MCF-7 mammospheres.

Additionally, berberine also inhibits the activity of ABC transporters capable of providing multiple drug resistance in cancer stem cells (Jang et al., 2021). Minimizing chances of multiple drug resistance, specifically in CSCs, makes berberine an alternative source of cytotoxic agents that provide resistance to cancerous cells. A female mice model system in which MCF-7 breast cancerous cells were injected and subsequently treated with different doses of berberine formulations showed synergistic properties. An amalgam of berberine liposomes amount 10 mg/kg with 10 mg/kg of taxol liposomes proved efficient in decreasing the tumor size in these model mice by eighty-five percent in contrast to the control after the period of twenty-one days (Ma et al., 2013). Therefore, berberine could be utilized in targeting CSCs or in supplement with other traditional CT (chemotherapeutic) agents.

Quercetin

Quercetin, a flavonol that commonly occurs in different types of medicinal plants. It is a flavonol. Quercetin acts as an anti-inflammatory and anti-oxidant agent generally involved in induction apoptosis in different kinds of malignant cancerous cells. Quercetin has been involved in a blockage of many singling processes linked with the genesis and sustainment of different human carcinoma, which includes low regulation of P-53, inhibition of enzyme activity of tyrosine kinase, inhibition of HSP proteins, and further involve inactivating type second estrogen receptors regulation process (Lamson and Brignall, 2000). Quercetin has gained significant importance as a drug for targeting CSC. Quercetin has not only showed to block the proliferation of prominin-1 colon cancer cells at a minute concentration of 75 micromoles, but also it is involved in developing the sensitiveness of cancerous tissues to adriamycin. Generally, it was reported that when quercetin 50 micromoles given in combination with adriamycin dosages were found efficient at blocking cancer cells proliferation *in vitro* condition than adriamycin dosages thrice concentrated devoid of quercetin metabolite (Atashpour et al., 2015). This research describes the important role of quercetin and other secondary metabolites, which together act with chemotherapeutics agents applied to eliminate cancer cells. The low concentration of chemotherapeutic drugs in combination with different natural compounds like quercetin may provide less off-target toxicity while also helping induce programmed cell death in cancer stem cells, hence improving patient outcomes, reducing risk factors involved cancer recurrence, and prevention of metastasis. Many cancer stem cell models have been used as a target by induced quercetin activity that includes CD44+/CD133+ prostate cancer stem cells. At a 20 micromoles amount, quercetin reduces the sustainability of prostate tumor cells cultured in a non-adhering vessel as well as reduces migration, invasiveness, and colony producing potent of CD44+/ prominin-1 prostate cancer stem cells (Tang et al., 2010). In important research, quercetin showed a synergetic effect with epi-gallocatechin gallate, catechin generally occurs in beverages, synergistically maximizing its impact on prostate cancer cells. As it is observed in the case of different NP's, however, quercetin is poorly soluble, poorly permeable, and has reduced bioavailability (Cai et al., 2013). In high general concentration of quercetin generally triggers a biochemical response in supplement with these problems further drug delivery technique to enhance lifetime concentration of these substances at neoplasm.

Polyynes

Falcarindiol and falcarinol are secondary metabolites generally found in parsley, carrot, and Oplopanaxhorridus, which are generally associated with ginseng. In a research, it was described that falcarindiol could stop GSK3β (enzyme) in an ATP uptake in a non-competitive way (Yoshida et al., 2013). Falcarinol and

its related compounds act as a potential inhibitor of BCRP, i.e., ABCG2 (Tan et al., 2013). The action of these organic metabolites against cancer stem cells signifies a bright future in advanced cancer studies.

CONCLUSION

The conventional system of chemotherapy includes radiation therapy and the usage of synthetic drugs, which were effective against various forms of tumor cell types, but it doesn't perform well against Cancer stem – cell specialized targets that cause tumor reoccurrence and metastasis. Many natural products that are usually found in various foodstuffs have shown the capability to regulate the pathways responsible for cancer stem cell activity and inhibition. Therefore, natural products should be explored and properly screened as potent chemotherapeutic agents, as supplementary treatments for drugs already in use based on their clinical efficacy, and cancer-preventing compounds with a special focus on their capacity to target cancer stem cells. Furthermore, limited bioavailability and increased metabolic activity of these natural products, drug discovery process together with continuous efforts to generate strong formulations and other delivery techniques should be taken into consideration.

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Chapter 9
Natural Products and Their Bioactive Compounds as Chemotherapeutics:
Natural Products to Prevent Drug Resistance in Cancer Chemotherapy

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ABSTRACT

Cancer is the second world's deadliest disease. Despite substantial advancements in medical technology for cancer therapies, cancer mortality remains greater than projected, and cancer treatment requires additional study. The research carried out in natural products is due to the presence of bioactive compounds, unique structures, and mechanistic actions. Prevention of drug resistance in chemotherapy is predominant in the usage of anticancer drugs. Clinical chemotherapeutic medicines work by causing cancer cells to die, the majority of which is apoptotic. Another way to combat drug resistance in cancer therapy is circumventing apoptosis by targeting non-apoptotic cell death. The authors discussed in this chapter both apoptotic and non-apoptotic cell death.

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INTRODUCTION

Cancer is a common fatal disease. The people who are affected by cancer have felt as short life period and not a good quality of life. It affected more than 10 million people in the world per year. World Health Organisation (WHO) reported that it affects one in five men and one in six women in their life and kills one in eight men and one in eleven women. It is a huge burden on society. Cancer is a multifaceted and refractory illness produced by a complex interplay of local tissue microenvironmental and hereditary variables (Klemm and Joyce, 2015). Cancer is a collection of disorders characterized by uncontrolled and aberrant cell division, as well as malignant characteristics such as invasion and metastasis. Cancer is a global issue with significant morbidity and fatality rates.

Surgery, chemotherapy, and radiotherapy are the most common cancer treatments today. While surgery may not always be able to eliminate all cancer cells from the human body, both chemotherapy and radiotherapy kill the normal cells in the body. This is the biggest side effect in cancer treatment. For more than half an epoch, natural products have been broadly scrutinized to prevent drug resistance in cancer chemotherapy due to their astonishing diversity in the chemical field. Mostly natural products derived from plants and animals have been the source for all pharmaceutical companies. Natural products have recently continued to serve as exemplars for biologically active molecules, especially for cancer treatment (Cragg and Pezzuto, 2016).

The purpose of cancer treatments is that:

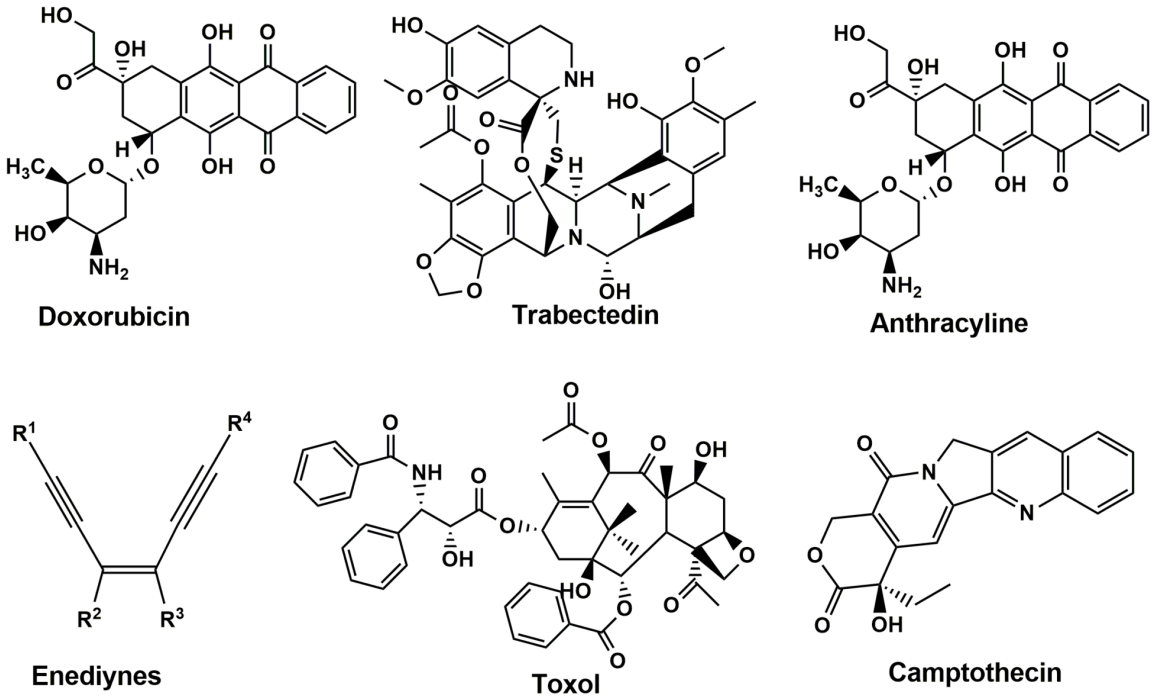
- It recovers health of the human beings.
- The disease is conveyed under control due to the improvement in the immune system.
- Prevention of reoccurrence of cancer is carried out.
- The symptoms are reduced.

Depending on the type of cancer, there are many types of cancer treatment. Some cancer patients will just require one treatment. Most people, on the other hand, receive a mix of therapies, such as surgery combined with chemotherapy and/or radiation therapy. They are frequently used in tandem. Surgical treatment, chemotherapy, irradiation, and hormone therapy are the most common types of cancer treatment. For clinical treatment, chemotherapy is broadly used. Chemotherapeutic pills destroy swiftly proliferating malignant cells. Cancer chemotherapy is the customary core therapeutic usage. Prevention of drug resistance in cancer chemotherapy is predominant in the usage of anticancer drugs. Because of their distinct chemical structures and bioactive characteristics, natural goods are effective against medication resistance. The discovery of drug-resistant proteins and drug-efflux inhibition activities is the mainstay of cancer chemotherapy (Robey *et al.,* 2018). Drug resistance must be managed carefully for chemotherapy to be effective. Natural goods deserved to dazed medication confrontation, according to the scientific and industrial communities.

Common treatment strategies are including radiotherapy and/or chemotherapy with surgery, resulting in a high treatment failure rate. For example, doxorubicin is used as a chemotherapeutic agent for cancer therapy which persuades the cancer cells as well as normal cells also. There is continuous development in the treatment of cancer for rectifying the side effects in the body. Paclitaxel which is derived from the bark of *Taxus Breifolia* is one of the most successful tales in plant-based natural products (Ashraf, 2020). Trabectedin, anthracycline, and enediynes which are derived from the marine environment and microbiological organisms have also been used as high therapeutic agents. Currently, 10,000 plant species

are used in the medicinal field which is available in rain forests and grasslands also. Out of 93 in 174 new compounds which are derived from natural products have been commercialized for cancer treatment in the 1980s (Amaral *et al.,* 2019). From 1981 onwards, new novel drugs which are used for cancer treatment are mostly natural products, because, they contain bioactive compounds. National Cancer Institute (NCI) has identified two anticancer drugs which are derived from natural products during the periods of 19th century are camptothecin and taxol. Figure 1 shows chemotherapeutic agents used for cancer therapy.

Figure 1. Chemotherapeutic agents



DRUG RESISTANCE

Cancer is the major reason for evanescence universal disease for the increasing mortality rate of 8.2 million death/year (Rajesh *et al*., 2015). The risk of cancer is raised by various factors like corpulence, meager food, cigarette smoking, radioactivity, environmental noxious waste, the privation of corporal action, and oldness. Cancer harms the genetic factors swerving and/or unswervingly in mishmash with prevailing genomic metamorphosis in cells (Anand *et al*., 2008). Cancer treatment is carried out with surgery, radiotherapy, and chemotherapy in which chemotherapy is mostly used for cancer treatment (MacDonald, 2009). Hitches are created in the body by killing healthy cells with cancerous cells also (Carelle et al., 2002). Cancerous death is not reduced due to drug resistance itself because it obstructs the patient's diagnosis if there is continuous improvement in chemotherapy (Shaffer et al., 2012). Drug resistance is the main cause for 90% of death of cancer people.

In general, medication conflict is obsessed by 2 classifications: innate besides assimilated. Cancers thru inherent struggle to chemotherapy develop an impervious phenotype afore they are exposed to any chemotherapeutic agents, making treatment for these tumors useless. Most acquired resistance cancers respond to treatment at first but then grow resistant to similar medicines (Wang et al., 2010). Multidrug resistance (MDR), both intrinsic and acquired, can reduce the efficiency of chemotherapy and has arisen as a serious problem in cancer treatment (Longley and Johnson, 2005). Nearly 90% of ovarian cancer patients perish as a result of drug resistance. Palliative confrontation contrivances have been thoroughly researched and new anti-resistance therapeutic techniques should be created. Figure 2 shows various mechanisms that are also responsible for MDR in cancer cells.

FACTORS AFFECTING MULTIPLE DRUG RESISTANCE

Intrinsic Factors

Heterogeneity of tumours

Heterogeneity within tumours able to be seen in a various echelons of tumor and attributed on variety of variables which predominantly befall at the cellular level. This refers to the formation of regular variations that are influenced by genetic, epigenetic, transcriptomic, and proteomic features. Metamorphoses, genetic factor augmentations, obliterations, chromosomal reshuffles, reordering of hereditary rudiments, translocations, and microRNA alternation are all examples of genotypic alterations. In cancer, genomic instability leads to a high amount of intercellular genetic heterogeneity. Epigenetic variables such as miRNA, transcriptome, and proteomic heterogeneity can represent cubicle sequence stage, stochastic variances across compartments, or categorized organisation of compartments, bestowing to the tumor stanch chamber philosophy (Benner *et al.,* 1991, Arora *et al.,* 2013, Gupta *et al.,* 2011, Kreso *et al.,* 2013 and Nathanson *et al.,* 2014). Intrinsic factors are the changes that cause tumour heterogeneity.

Tumor microenvironment

The importance of the tumour microenvironment discussions which is primary cause of relapse and incurability of many malignancies is gaining traction. Usual stromal chambers (SC), extracellular milieu (ECM), and fathomable substances such as cytokines and development features all play a role in the tumour microenvironment. Unswerving cell connection arbitrated by drug resistance is mediated via lump-lump chamber announcement, polyp-stromal cubicle communiqué, and lump-ECM boundary (Li and Dalton, 2006). Furthermore, cytokines such as growth factor (GF) generated afford extra gestures for tumour cell survival and expansion.

EXTRINSIC FACTORS

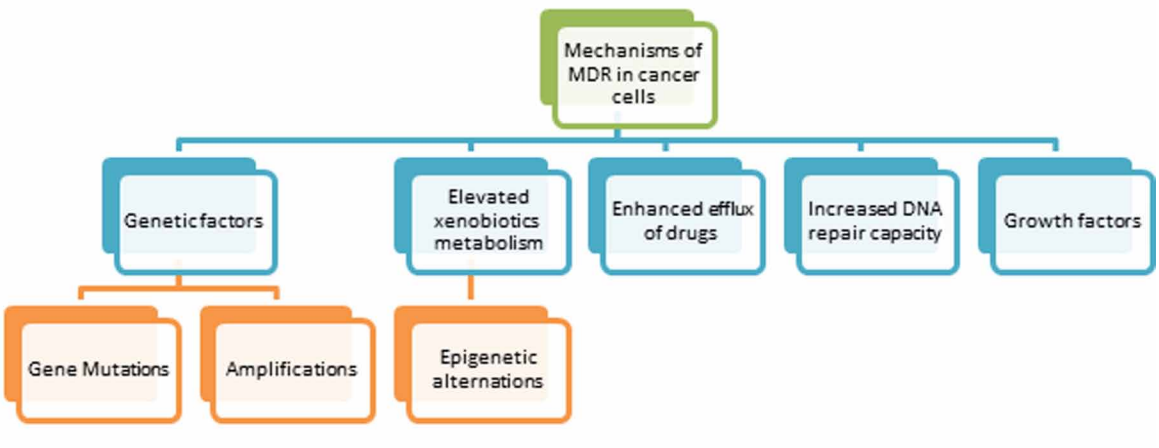
pH, hypoxia, and paracrine signalling connections with stromal and additional tumour cells are examples of extrinsic variables (Gatenby *et al.,* 2010 and Junttila and de Sauvage, 2013). These aspects alter,

Table 1. Chemotherapeutics for drug resistance

S. No.	Class	Compounds	Examples
1.	Alkylating agents	Oxazsaphosphorines	Cyclophosphamide ifosfamide
		Nitrogen mustards	Busulfan Chlorambucil Melphalan
		Hydrazine	Temozolomide
		Platinum based agents	Cisplatin Carboplatin Oxaliplatin
		OFF-ON Type alkylating agents	Vinyl-quinazolinone
2.	Antimetabolites	Pyrimidine antagonists	Cytarabine 5-flurouracil Gemcitabine Capecitabine
		Purine antagonists	Fludarabine
		Purine analogs	6-mercaptopurine Azathioprine Cladripine
		Antifolates	Methotrexate Pemetrexed Pralatrexate
		Ribonucleotide reductase inhibitors	Hydroxyurea
3.	Topoisomerase I Inhibitors		Irinotecan topotecan
4.	Topoisomerase II Inhibitors		Etoposide Teniposide
		Anthracyclines	Idarubicin Daunorubicin Doxorubicin
5.	Mitotic spindle inhibitors	Taxanes	Docetaxel paclitaxel
		Vinca alkaloids	Vincristine Vinblastine
6.	Other chemotherapeutic agents	Enzymes	L-asparaginase
		Proteasome inhibitors	Bortezomib
		Tyrosine kinase inhibitors	Imatinib Erlotinib
		Antibiotics	Bleomycin Actinomycin D

enhance, or decrease genetic factor merchandises that are openly linked to medication resistance and a meagre prognosis.

Figure 2. Mechanisms of MDR in cancer cells



REVERSE DRUG RESISTANCE

Drug resistance is reversed by natural products that regulate drug-resistant proteins. The major fraction of prescription battle MDR was first hypothesized in 1976. Flat of antineoplastic medicines is reduced by the archetypal MDR in multidrug-resistant cells. Clan of ATP binding cassette (ABC) juggernauts contains these transmembrane transporters (Dean et al., 2001). In these, 49 kinds are notorious in human beings among 100. P-glycoprotein (P-gp) is the best wilful species (Choi, 2005). It is the result of the humanoid MDR1 inheritable factor. It has around1280 amino acids, 2 ABCs, and 2 transmembrane provinces. Doxorubicin, vincristine, daunorubicin, paclitaxel are regulars of it. It can perceive and bore drugs through the plasma membrane. The stimulation of ATP-tie purviews and hydrolysis of ATP due to binding of it varies the nature of it and upshots in drug efflux (Illmer *et al.,* 2004).

The reverse effect of MDR is carried out by natural products like tanshinone, tetrandrine, quercetin, grape-seed polyphenols, tea polyphenol, etc., which have introverted the P-gp transference structure (Li *et al.,* 2014). These natural products are amassed the intracellular focus of chemotherapeutic drugs by constraining P-gp efflux to impel effect. MDR-associated protein (MRP) is a new ABC superfamily supporter which was discovered in 1992. Some phenomenon such as glutathione, glucosylation, conjugation, sulfation, glucuronidation, etc., is arbitrated by MRP which conveyances negatively charged drugs and natural products also (Borst *et al.,* 2000). For example, curcumin, quercetin, baicalein, etc., impede MRP and inverse MDR (Efferth *et al.,* 2002).

Natural products such as doxorubicin, daunorubicin, and teniposide encourage drug resistance through Breast cancer-resistant protein (BCRP) (Austin Doyle and Ross, 2003), and cyclophosphamide, and doxorubicin persuades the resistance by lung resistance protein (LRP) (Burger *et al.,* 2003). Clinical chemotherapeutic medicines work by causing cancer cells to die, the majority of which is apoptotic. Drug-resistant cells are protected against harmful medicines, free radicals, and radiations by the many mechanisms involved in drug resistance and so dodge apoptosis (Igney and Krammer, 2002). In addition to blocking MDR and associated proteins to increase chemotherapeutic intracellular concentrations, circumventing apoptosis by targeting nonapoptotic cell death could be another way to combat prescription confrontation. Table 2 lists the natural products which induce apoptosis.

Table 2. Natural Products using for inducing apoptosis

S. No.	Class	Compounds	Source	Mode of action
1.	Flavones and isoflavones	Geninstein	Plant derived	Induce apoptosis
		Tangeretin	Citrus peels	
2.	Naphthoquinones	Shikonin	Lithospermum	Produces antiproliferative and pro-apoptotic changes associated with pyruvate metabolism
3.	Allyl disulfides	Di and tri allyl sulfides	Garlic derived	Induce apoptosis
4.	Curcumin and curcumin derivatives	Curcumin	Plant (Turmeric) derived	Induces apoptosis

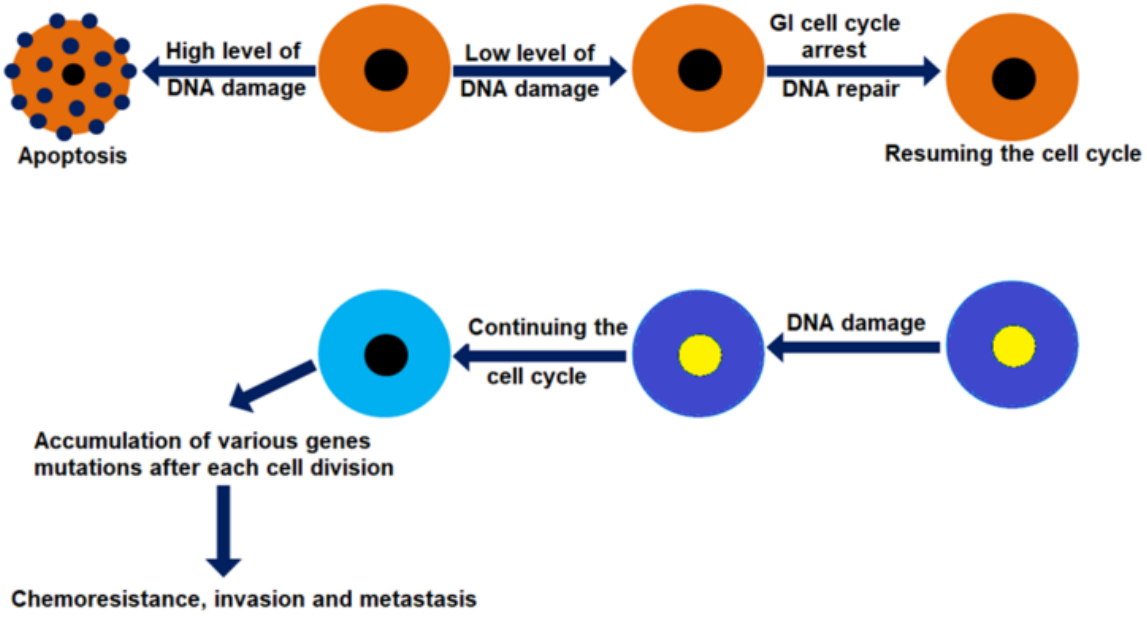
ROLE OF INFLAMMATORY PATHWAY INTERACTIONS

Multidrug resistance to chemotherapeutics is one of the most serious problems in cancer treatment. Different circumstances have been shown to tune the expression and activity of MDR transporters in recent investigations. Inflammation, for example, occurs in the most tumour microenvironment through a complicated cytological process and chemical reactions; it can play a crucial role in cancer development and can change the expression and function of MDR transporters. Cytokines, interleukins, and prostaglandins are strong inflammatory mediators that can affect MDR expression at transcriptional and post-transcriptional levels in most human cancer cells and tissues, and may help to balance chemotherapeutic drug bioavailability. Because most cancer cases are accompanied by inflammatory reactions, glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used combination chemotherapies in a range of cancer treatment protocols. These drugs, in addition to their anti-inflammatory properties, have a variety of modulatory effects on MDR-mediated drug resistance via unique pathways. The regulatory mechanisms are primarily influenced by a number of parameters, including cell and MDR-protein types, pharmacokinetics, and pharmacogenetics. The discovery of networks between inflammation and multidrug resistance will aid in the treatment of malignant malignancies and the reduction of cancer death rates in the clinic.

SIGNALING PATHWAYS

Cancer stem cells have long been thought to represent attractive therapeutic targets. These cells have the ability to self-renew and differentiate, and they have a role in a variety of cancers, including recurrence, metastasis, heterogeneity, multidrug resistance, and radiation resistance. Several pluripotent transcription factors, such as OCT4, Sox2, Nanog, KLF4, and MYC, govern the biological activity of CSCs. In addition, many intracellular signaling pathways, such as Wnt, NF-κB (nuclear factor-κB), Notch, Hedgehog, JAK-STAT (Janus kinase/signal transducers and activators of transcription), PI3K/AKT/mTOR (phosphoinositide 3-kinase/AKT/mammalian target of rapamycin), TGF (transforming growth factor)/SMAD, and PPAR (peroxisome proliferator-activated receptor), as well as extracellular factors, such as vascular niches, hypoxia, tumor-associated macrophages, cancer-associated fibroblasts, cancer-associated mesenchymal stem cells, extracellular matrix, and exosomes, have been shown to be very important regulators of CSCs.

Figure 3. DNA damage pathway for normal cell and cancer cell



NONAPOPTOTIC CELL TARGETS

By focusing on non-apoptotic cell death, natural products can circumvent medication resistance. For spans, apoptosis was thought to be the only way for controlled programmed cell death (PCD). Other types of PCD have lately been discovered, including necroptosis and autophagy. Given that the majority of chemotherapeutic medications cause cancer cells to die by inducing apoptosis, and confrontation of apoptosis is the ultimate fate of it. Other PCDs could provide novel ways to get around it. Few natural compounds and their derivatives, interestingly, are dynamic tempters of them. The Discovery of it aids in the research and development of new anticancer drugs.

Necroptosis

Necrosis is an unfettered, fortuitous cell bereavement. Necrostatin-1 and its equivalents are precise chemical inhibitors. These inhibitors are redefined an arrangement of synchronized necrosis is called necroptosis (Degterev *et al.,* 2005). Various triggers can cause necroptosis, including demise receptor ligands, epidemiologic and microbial contagion, cytokines, and substances (Robinson *et al.,* 2012, Upton *et al.,* 2012 and Thon *et al.,* 2006). These triggers can ordinarily impasse to death receptors or Toll-like receptors on cell membranes. Triggering necroptosis in two stages: an instigation stage, a cell gets a spur, it begins to form multiplexes; the cell demise linked with the damage of it and organelle veracity ends with convinced in the execution phase (Han *et al.,* 2007 and Ermolaeva *et al.,* 2008).

Receptor-Interacting Protein 3 (RIP3) is an imperative constituent in usual necroptosis. The mixed-lineage kinase domain-like protein (MLKL), a connector protein for the necrosis motion that can affect membrane veracity, is phosphorylated by RIP3's kinase activity (Moriwaki *et al.,* 2015). The production of necroptosis is a novel technique for combating cancer's apoptosis resistance. Shikonin, a naturally

befalling naphthoquinone, has been shown to cause it in MCF-7 breast cancer cells by dramatically boosting RIP3 expression as well as mitochondrial Reactive Oxygen Species (ROS) generation. Shikonin bypasses drug resistance that is regulated by drug transporters. Several shikonin analogs induce necroptosis, which can be used to overcome medication resistance (Xuan and Hu, 2009).

While it may offer a way to overawed confrontation, various concerns developed necessitate additional research. Since the incidence of it studied on the base of impeder action of RIPK1 deters, the precise molecular signaling pathways remain unknown. RIP1, a multifunctional molecule is an inducer of apoptosis but not an exact negotiator of it (Ye *et al.,* 2012). Induced aseptic inflammations are also a worry due to the discharge of intracellular constituents instigated by the rupture of the cell membrane (Harris *et al.,* 2017). The number of these persuaders is significantly lower than apoptosis tempters.

Autophagy

Autophagy is a cytoplasmic macromolecule and organelle breakdown process involving twofold sheath-destined edifices and lysosome blend (Zhang *et al.,* 2012 and Mizushima, 2007). Autophagy was first recognized as an essential process when cells were starved or stressed (Wang *et al.,* 2011). Autophagy is also recognized as autophagic cell demise when dealing with extreme stress (Wang *et al.,* 2011). The inhibitory action of autophagy inhibitors such as 3-methyladenine and chloroquine (CQ) implies that it enthusiastically contributes to cell endurance and propagation, despite differing opinions on its roles in cell survival and death. Autophagy is triggered by a variety of circumstances, and its regulation is complex (Mizushima, 2007). Many types of cells are strongly induced to autophagy by total amino acid consumption or serum starvation (Kanazawa *et al.,* 2004). Some growth factors, such as the hematopoietic growth factor interleukin-3 (IL-3) repression, regulate autophagy through regulating nutrients. In addition, autophagy is regulated in vivo by the endocrine system, particularly insulin (Kanazawa *et al.,* 2004). The mammalian target rapamycin (mTOR) is convoluted in evolution features & nutritional gestures. It is a negative device of it (Kondo et al., 2005) and is the best-studied pathway in autophagy. Few amino acids decrease it without relying on mTOR (Kanazawa *et al.,* 2004 and Mordier et al., 2000). The autophagy process begins with the development of the autophagosome, a characteristic double-membrane organelle regulated by the autophagy-related gene (ATG) proteins (Kang *et al.,* 2011, Yousefi *et al.,* 2006 and Mizushima *et al.,* 2011).

Before autophagosomes and lysosomes merge, autophagosomes wrath with endosomes to generate amphisomes, it serves as a burgeoning arrangement for autophagosome-lysosome meld (Dall'Armi *et al.,* 2013). Autolysosomes (or autophagolysosomes) break down the inner membrane and encapsulated components of autophagosomes via lysosomal hydrolases once the budding forms fuse with lysosomes. Amino acids are transferred to the cytosol for reprocessing after lysosomal/vascular macromolecules have degenerated (Levine and Kroemer, 2008). After incomings of proteins and organelles overdoes the capability, excessive or persistent autophagy can lead to cell death (Sun, 2011). Autophagic cell death is induced by arsenic trioxide (As_2O_3), an inorganic chemical with significant efficacy in the treatment of acute promyelocytic leukemia (APL) (Qian *et al.,* 2007 and Goussetis *et al.,* 2010). In glioma cell lines, As_2O_3 also triggers it by upregulating the mitochondrial cell death protein BNIP3 (Kanzawa *et al.,* 2005 and Kanzawa *et al.,* 2003). Resveratol, a natural polyphenolic phytoalexin, induces autophagy leukemia cells (Puissant *et al.,* 2010). Oridonin (Cui *et al.,* 2007) and allicin (Chu *et al.,* 2012) also stimulate autophagic cell death. Autophagy's role in cancer, on the other hand, has both benefits and

drawbacks. This mechanism also encourages cell survival and multiplication, both of which contribute to anticancer treatment resistance (Chen *et al.,* 2010).

Autophagy is used by cancer cells in advanced stages to subsist ecological vicissitudes such as reduced oxygen and nutrition levels, as well as to chunk the apoptotic alleyway and reduce the paraphernalia of anticancer medications (Wang *et al.,* 2011). Drug-resistant tumor cells can be resensitized to chemotherapy by inhibiting autophagy using molecules like 3-methyladenine, hydroxychloroquine, and bafilomycin A1 or by knocking down short hairpin RNA (shRNA) (Qadir *et al.,* 2008 and Boya *et al.,* 2005). As a result, inhibiting autophagy may be a viable therapeutic method for reducing medication conflict. Hydroxychloroquine was licensed as the autophagic inhibitor. This medicine increases the responsiveness of resistant mammary tumors to antiestrogens, resulting in increased apoptotic death of cancer cells (Cook *et al.,* 2014, Clarke *et al.,* 2009 and Cook *et al.,* 2012). Several strategies, such as inducing autophagic cell bereavement and inhibiting pro-survival autophagy, aid in the use of autophagy in melanoma treatment. The ultimate upshots of medical tribunals combining the autophagy detour CQ with chemotherapeutics will afford even more compelling use in medication improvement.

Oncosis

Cell enlargement, organelle puffiness, and augmented sheath penetrability are all signs of oncosis, which is a type of cell death. The deactivation of ionic impels causes these morphological characteristics (Vazquez-Nin *et al.,* 2011). In oncosis, a quick drop in intracellular ATP echelons is a significant physiologic event. Energy reduction and ionic deflate inactivation in the plasma membrane result in a significant decrease in mitochondrial exhalation and ATP generation, as well as changed ionic fluidities and cell capacity instruction (Vazquez-Nin *et al.,* 2011). The anarchic ion impel raises the quantity of calcium ions in the mitochondria, allowing cytosolic phospholipase A2S to translocate to cell membranes and compromise membrane integrity (Vazquez-Nin *et al.,* 2011 and Weerasinghe and Buja, 2012), Calpains (Vazquez-Nin *et al.,* 2011 and Liu *et al.,* 2004) and uncoupling protein 2 (UCP-2), a protein widely expressed in the inner mitochondrial membrane (Mills et al., 2002), both play important roles in oncosis. Calpain activity is increased, which inhibits caspase bustle and slashes Bid and other molecules to modulate mitochondrial sheath potential and cause cell bereavement (Chen et al., 2001). Stimulation of cell exterior receptors can also initiate oncosis.

Sanguinarine, a benzo phenanthridine alkaloid derived from the *Papaveraceae* family, causes cancer cells to undergo at least three different forms of cell death: apoptosis, autophagy, and oncosis (Weerasinghe and Buja, 2012, Gu *et al.,* 2015 and Pallichankandy *et al.,* 2015). In cancer cells, such as leukaemia (Weerasinghe *et al.,* 2006 and Weerasingle *et al.,* 2001), cervical cancer (Ding *et al.,* 2002), and breast cancer (Weerasinghe and Buja, 2012), sanguinarine causes a lot of oncosis. In human K562 leukemia and squamous cell carcinoma KB cells, solamargine derived from solanum incanum promotes oncosis (Sun *et al.,* 2011). Artesunate, a semisynthetic derivative of artemisinin (Du *et al.,* 2010), and rosin from pinus species oleoresin (Luo et al., 2016 and Zhou et al., 2013) are two more natural oncosis inducers. However, there is a scarcity of information about the molecular signaling mechanism, regulation, and physiological and medical importance of oncosis. Oncosis, being a nonapoptotic cell death mechanism, could give an alternative option for improving drug resistance.

Methuosis

Methuosis caused in glioblastoma and gastric cancer cells by constitutive Ras signaling activation was discovered more than a decade ago (Maltese and Overmeyer 2014). Methuosis is marked by extensive vacuolization and cell rupture. Only a few methuosis inducers have been identified: in glioblastoma cells, the chalcone-related small molecule 3-(2-methyl-1H-indol-3yl)-1-(4-pyridinyl)-2-propen-1-one (MIPP) promotes methuosis (Overmeyer *et al.,* 2011). In cancer cells, ginsenoside, curcumin, and quercetin cause cytoplasmic vacuolization with methuosis-like features (Shubin *et al.,* 2016). Methuosis-induced cell death has been seen in MDR malignancies (Overmeyer *et al.,* 2011 and Bishayee et al., 2016). Its therapeutic potential is revealed.

Table 3. Natural Products using for Stimulation of non-apoptotic cell death

S. No.	Non-apoptotic cell death	Natural inducers
1	Necroptosis	Shikonin and its analogs
2	Autophagy	Ar_2O_3, *G. lucidum triterpene*, Resveratrol, Oridonin, Allicin
3	Oncosis	Sanguinarine, Solamargine, Artesunate, Rosin
4	Methusis	Chalcone; Ginsenoside; Curcumin, Quercetin

Overcome Drug Resistance

Drug efflux, inhibition of cell death, detoxification, DNA damage repair, drug target switching, stem cells, and epithelial to mesenchymal transition are all examples of biological mechanisms that contribute to cancer chemoresistance (Housman *et al.,* 2014 and Wu *et al.,* 2014). Drug efflux, cell death inhibition, and detoxification are all topics that are frequently researched. Drugs can be expelled from cancer cells and the intracellular drug concentration can be reduced, thwarting drug injuriousness. The humanoid genome encrypts 48 ATP binding cassettes (ABC) proteins, which are divided into ABCA to ABCG 7 subgroups, with 15 of them linked to medication confrontation. These proteins are hypothesized for important in the improvement of cancer cell chemoresistance (Vadlapatla *et al.,* 2013). Most well-studied ABC proteins include MDR1 (P-glycoprotein), multidrug resistance-associated proteins (MRPs), and breast cancer resistant protein (BCRP). Table lists families of human ABC transporters and their functions.

Chemotherapy-induced apotosis is the most common kind of cell death. Apoptosis has two well-established routes. The mitochondria are at the hub of the intrinsic route. Apoptotic gestures attract pro-apoptotic molecules like Bax to mitochondria, forcing mitochondria to relieve cytochrome C, which triggers cell death via downstream caspases, which are apoptosis effectors. The extrinsic route is triggered when a ligand binds to a cell surface death receptor, activating caspase-8 and subsequently downstream caspases. Natural products justify being able to combat medication resistance, according to the scientific and industrial people. There are four types of revisions to overwhelmed cancer treatment skirmish:

- Using cancer cell line models through *in vitro* study
- Using serum samples from animal fed natural products in a serum pharmacology study
- Using animal models containing tumor xenografts or transplantable tumor cells in an *in vivo* study

Table 4. List of families of human ABC transporters and their functions

S. No.	ABC transporter Family	ABC transporter	Major function
1.	ABCA	ABCA1	Efflux of cholestrol
		ABCA2	MDR
		ABCA3	Surfactant Secreation
		ABCA4	Efflux of N-retinylidene phosphatidylethanolamine (PE)
		ABCA5	Urinary diagnostic marker for prostatic intraepithelial neoplasia (PIN)
		ABCA6	MDR
		ABCA7	Efflux of cholestrol
		ABCA8	Transports of some lipophilic drugs
		ABCA9	Might play a role in monocyte differentiation and macrophage lipid homeostasis
		ABCA10	Chloestrol-responsive gene
		ABCA12	Has implications for prenatal diagnosis
		ABCA13	Inherited disorder affecting the pancreas
2.	ABCB	ABCB1	MDR
		ABCB2-TAP1	Peptide transport
		ABCB3-TAP2	Peptide transport
		ABCB4	Phosphatidylcholine (PC) transport
		ABCB5	Melanogenesis
		ABCB6	Iron transport
		ABCB7	Fe/S Cluster transport
		ABCB8	Intracellular peptide trafficking across membranes
		ABCB9	Located in lysosomes
		ABCB10	Export of peptides derived from proteolysis of inner-membrane proteins
		ABCB11	Bile salt transport
3.	ABCC	ABCC1	Drug Resistance
		ABCC2	Organic anion efflux
		ABCC3	Drug Resistance
		ABCC4	Nucleoside transport
		ABCC5	Nucleoside transport
		ABCC6	
		ABCC7	Chloride ion channel
		ABCC8	Sulfonylurea transporter
		ABCC9	K(ATP) Channel Regulation
		ABCC10	
		ABCC11	
		ABCC12	
4.	ABCD	ABCD1	VLCFA Transport Regulation
		ABCD2	
		ABCD3	
		ABCD4	
5.	ABCE	ABCE1	Oligoadenylate binding protein
6.	ABCF	ABCF1	
		ABCF2	
		ABCF3	
7.	ABCG	ABCG1	Chloestrol Transport
		ABCG2	Toxin Efflux, Drug Resistance
		ABCG4	
		ABCG5	Sterol transport
		ABCG8	Sterol transport

- Comparison of a clinical trial of the patients who received natural products in addition to conventional chemotherapy to those who received conventional treatment alone.

In Vitro Study

Anti-drug resistance action has been observed in natural items all over the world. By blocking medicine juggernauts, cell purification ability, or cell apoptosis sympathy, compounds utilized *in vitro* studies were able to astounded medication conflict at non-toxic or subtoxic concentrations in a dosage-needy. In bladder cancer T24/ADM cells, Wang and colleagues found that doxorubicin improves medical compassion by 2.5 times (Wang *et al.,* 2012). According to Nong and associates (Nong *et al.,* 2010), the antidrug sensitivity of evodiamine is increased 11.4 times in the A549/DDP cell line. Celastrol increases chemo drug sensitivity in K562/A02 cells by 117.9%, accompanied by a considerable rise in intracellular medical deliberation and a drop in MDR1 protein level (Hu *et al.,* 2011). Embelin was reported to boost drug-resilient K562 cells' susceptibility to daunorubicin by 7.5 times (Hu *et al.,* 2011).

Serum Pharmacology

A serum pharmacological investigation, at least in part, presents a way to solve the problem (Hiroko *et al.,* 1987). Animals are fed chemicals and herbal extracts for a brief period in this sort of assay, and blood tasters are taken for bioactivity assays *in vitro* cell line replicas. The results are more likely to reflect chemical bioactivity *in vivo*. Compounds are administered to animals in amounts that are comparable with the quantity per unit of body weight. The serum is frequently used in cell culture at foci ranging from 5% to 20% by volume. Changweiqing's antidrug resistance impact was reported by Deng and colleagues discovered that serum samples from rats could boost the kindliness of medical resilient HCT8/V cells to cisplatin by 13 times *in vitro* (Deng *et al.,* 2008) It's also been seen in the KB-A-1 oral epidermoid carcinoma cell line. It improved the drug resistance cells' doxorubicin sensitivity to 5.2 times in a dosage quantity (Xu *et al.,* 2005). The sensitivity of A549/DDP cells to cisplatin can be increased 2.5 times by serum from animals treated with Wenxia formula extract (Ji *et al.,* 2006).

In Vivo Study

Natural products, herbal extracts, and formulations employed in vivo studies demonstrated powerful anti-drug resistance properties that were also used in clinical trials. By blocking the drug pump, herbal extracts overcome the tumor xenograft's treatment resistance. Zhang and coworkers reported that using oxaliplatin with Changweiquing extract reduced tumor size by 3.1 times compared to oxaliplatin in HCT116/L-OHP cells (Zhang *et al.,* 2012). Feng and collaborators showed that doxorubicin plus extract of Huatan Sanjie formula reduced tumor tissue by 4.8-fold in MCF-7/ADM cells in mice (Feng *et al.,* 2014). A single component with herbal extracts has been established to cause medical struggle *in vivo*. Epigallocatechin gallate enhances drug sensitivity to vincristine by 13 times in vitro research. It triples intracellular vincristine concentration while lowering intracellular MDR1 protein concentration. In a mouse model, the chemical greatly improves vincristine's anticancer impact while also lowering MDR1 and LRP mRNA levels in tumor tissues (Liang *et al.,* 2007). *In vitro*, cepharanthine is not harmful to EAC/ADR cells, but it can boost doxorubicin compassion by 13 times.

Clinical Studies

The eventual purpose of research is finally medical results. Patients are frequently separated into two groups in clinical investigations.

- Patients in the rheostat assembly receive standard chemotherapy,
- Patients in the treatment group receive standard chemotherapy combined with natural ingredients.

When Hu and colleagues discovered the treatment group had a smaller number of leukemia cells and a lower MDR1 protein glassy and a poorer diminution speed than the control group in bone marrow at the effect of *Fritillariae thunbergii* on 90 acute leukemia patients (Hu *et al.,* 2004). Li and colleagues looked examined the effect of *Fritillariae thunbergii* on 30 patients with acute leukemia who had a high level of MDR1 expression (Li et al., 2004). The treatment group had a lower MDR1 protein level, an upper medication retort amount, and a reduced percentage of leukemic cells in the bone marrow. Zhao and colleagues gathered 36 MRP protein-positive patients with desperate leukemia. They used instantaneous PCR to measure MRP and 2M mRNA levels in bone marrow cells, and patients with MRP/2M values of 0.3 or higher were deemed MRP positive. Patients who received ligustrazine injections were negative for MRP and had a minor with leukemic cells in their bone marrow.

ROLE OF NATURAL PRODUCTS TO OVERCOME MULTI DRUG RESISTANCE

The increase of ABC drug transporters causes multidrug resistance, which is a key stumbling block in clinical cancer chemotherapy. Direct inhibition of ABC transporters appeared to be the cheapest and most effective technique to fight this problem for numerous years. Unfortunately, finding a powerful, selective inhibitor to modify ABC transporters and restore drug sensitivity in multidrug-resistant cancer cells has been difficult. In a perfect world, candidate medications would be selective, potent, and generally non-toxic. Following the dismal results gained from inhibitors of the first three generations in clinical trials, many researchers have turned their attention to using natural compounds as building blocks for the development of the next generation of inhibitors. To be employed clinically, the first stage is to find natural compounds that are strong, selective, and relatively non-toxic (as opposed to the first three generations of inhibitors).

Natural products are an excellent source of a wide range of biologically active molecules for solving the problems that drug development projects face. Inhibitory effects have been found for terpenoids and phenolics. Essential oils are a complex blend of volatile molecules produced by aromatic and medicinal plants as a result of their secondary metabolism. These volatile compounds have long been employed in folk medicine for their antibacterial properties. A large number of studies on the use of essential oils and their components against multidrug-resistant bacteria like Acinetobacter baumannii, methicillin-resistant Staphylococcus aureus, Mycobacterium tuberculosis, and Pseudomonas aeruginosa show that these natural products have exceptional potential to prevent the spread of antibacterial resistance. In addition, combining essential oils and their components with medicines may boost bacterial susceptibility, limiting resistance.

The high frequency of multidrug-resistant bacteria in the etiologic structure of many infectious processes reduces the effectiveness of treatment and increases the risk of a negative infection outcome.

One of the most promising techniques for fighting multidrug-resistant bacteria is to combine antibiotics and other antimicrobial medicines. Combinations of antibiotics and natural antimicrobial compounds with complicated modes of action and various healing characteristics, such as plant essential oils, have a great therapeutic potential.

Many studies have indicated that essential oils have the ability to work in synergy with antibiotics in vitro. The main hypothesised reason for this positive impact is that certain essential oils inhibit efflux pumps, restoring the antibiotic's action. Further research on antibiotic-essential oil combinations against multidrug-resistant bacteria should be pursued in the future, with a focus on understanding the mechanisms of the resulting effect. Essential oil combinations with various antimicrobial agents, such as bacteriophages, nanoparticles, and quorum-sensing inhibitors, demand further attention and are worthy of future research.

Antibiotics are antimicrobial drugs that are used to treat bacterial infections. The recent epidemic of dangerous antibiotic-resistant bacteria highlights the urgent need for novel therapeutic options. Plant extract-plant extract, plant extract-essential oils, plant extract-conventional antibiotics, phytochemical-antibiotics, and essential oil-essential oil have been shown to have antibacterial action against various microbes using various methodologies, as well as synergistic effects. Infectious disorders produced by multidrug-resistant microorganisms, food borne diseases caused by food rotting microbes, and oral infections can all be treated with plant products and their active ingredients. Plant-derived products have the ability to limit microbial development in a variety of conditions, including disease therapy. Since the dawn of time, phytomedicines have been used to treat diseases and infections, but finding new phytochemicals and effective treatment procedures is critical in the fight against multidrug-resistant bacteria. Isolated substances such -mangostin, carnosic acid, epigallocatechin gallate, linalool, myricetin, novoimanin, -terpineol, and totarol have shown synergistic efficacy with antibiotics in the past.

Medicinal and aromatic plants, many of which generate essential oils used in folk and modern medicine, as well as the cosmetics and pharmaceutical industries, are all members of the Asteraceae family. Due to the inclusion of many active substances (e.g., terpenes and phenol-derived aromatic and aliphatic components) with distinct modes of action, essential oils exhibit a broad spectrum of bioactivity. Extensive research into the chemical components of Asteraceae species has resulted in the discovery of a number of compounds, including essential oils, with promising antibacterial properties.

PROBLEMS IN DRUG RESISTANCE

Directly or indirectly 80-90% of cancer deaths are due to drug resistance only. Scientific people have attained terrific encroachments in natural products like the usage of clinical treatments, innovation of new therapeutic drugs, etc., but defies continuous now also. Conversion of natural products into drugs is still perplexing due to the isolation of materials in large-scale industries, understanding the action of mechanisms, and improvement in the medical field. The occurrence of drug resistance, which is difficult in cancer chemotherapy, has also delayed the development of new innovative drugs. Scientists may have reached a tipping point in their efforts to better comprehend natural products and investigate their therapeutic potential. There have been numerous reports of substances with anticancer potential or specific structural benefits in studying druggable modalities. Many pharmaceutical companies throughout the world have scaled back or even abandoned their efforts in natural product drug development, preferring instead to rely on enormous libraries of chemically produced molecules or biologics.

Diligence and academics use a 'target first strategy to drug development, it may not be the greatest way to demonstrate the benefits of natural products in the treatment of complicated diseases like cancer. In most situations, inhibiting a single target does not result in ideal therapeutic effects and is disposed to developing confrontation. To improve the pace and success rate of natural product drug development, a variety of issues must be addressed.

1. How do you choose the right model to adequately expose natural ingredients' anticancer potential? Given the heterogeneity of cancer, it is widely assumed that a chemical that does not exhibit activity in one tumor model is not necessarily inactive in another. Furthermore, natural chemicals' anticancer effects could be due to their effects on the human being. It complicates the process of choosing the right archetypal.
2. How can targets and mechanisms be identified quickly? Accurate cancer treatment will necessitate a thorough understanding of natural chemical mechanisms of action. The current approaches are still technically hard and, for the most part, inefficient. Furthermore, because natural products frequently exhibit complex mechanisms, it is necessary to consider how to obtain a complete picture of the mechanism of natural chemicals.
3. How might the process of turning a potential candidate molecule into a marketable medicine be accelerated? The majority of bioactive nature products face challenges with large-scale manufacture. To tackle these challenges, ongoing conceptual improvement in cancer therapy and the application of breakthrough technology will be required.

SOLUTIONS AND RECOMMENDATIONS

Following that, several pharmaceutical companies worked to solve the issues of turning natural materials into medications. It is now possible in the discovery of drug efficacy and by minimizing the complexity of drug biological effects. With the recent explosion of information in cancer therapy and modern technologies, it is now possible to overcome obstacles in drug discovery efficiency, disclosing natural product direct targets, and resolving the complexity of multi-faceted pharmacological effects. Because of their diverse mechanisms, natural goods appear to have an edge in dealing with 'target first situations.

Artificial intelligence (AI) is becoming increasingly important in pharmaceutical research. Several techniques development initiatives and practical applications have been documented, indicating how AI is making its way into the drug discovery arena. To overcome the problems of both discovering bioactive natural compounds and understanding their processes, a growing trend is to use AI methodologies in natural product research.

FUTURE RESEARCH DIRECTIONS

Soon, many natural goods will continue to play an important role. Emergent healing perceptions and new-fangled skills work laidback to keep the profession growing. With increased knowledge of cancer's molecular changes, anticancer drug discovery is shifting away from phenotypic screening and toward objective-based screening in identifying medicines' well-defined mechanisms of action. Integrated target and phenotypic tests are predicted to better expose in this situation. The efficiency of drug hunting will be

improved by a comprehensive screen platform. Machine learning techniques in structure identification, categorization, confirmation simulation, library design, and activity prediction are at an early period. Natural compounds could undoubtedly modulate the Tumor microenvironment (TME) independently of the microbiota. combination strategy is a significant direction for natural product discovery in cancer therapy. Natural product adjuvant treatment with current regimens could be advantageous in many ways, including lowering side effects, overcoming medication resistance, and enhancing therapeutic response. The combination therapy technique is especially important for bioactive medicines, which are generally constrained by existing research models' moderate therapeutic effects yet have a decade of clinical experience.

CONCLUSION

Drug resistance accounts for a significant portion of cancer treatment failure. Despite efforts, there has yet to be a viable way to overcome cancer cell medication resistance. Natural products offer a large pool of potential medication candidates, as well as candidate molecules for overcoming drug resistance. Many natural compounds, either taken alone or in combination, be potential inhibitors of drug resistance in laboratory and clinical settings, providing new insights for the scientific and industrial communities. Some single chemicals, as well as herbal compounds and herbal formulations, have been utilized in clinical trials to treat a variety of ailments, including cancer. Drug resistance, particularly MDR, has been recognized as the most serious worry among oncologists and patients.

Natural products may contribute to the repair and maintenance of signaling networks' robustness by interacting with multiple targets. Controlling MDR to increase chemotherapeutic medication intracellular concentrations is a well-studied approach. The authors of this research propose a new approach that involves encouraging nonapoptotic cell death processes like necroptosis, autophagy, and oncosis. However, because the majority of the recently found PCDs are unknown, their potential worth, benefits, and drawbacks in the fight against drug resistance should be clarified. Future research could lead to the discovery of natural compounds that can be used to treat cancer cell treatment resistance in the clinic.

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APPENDIX: ABBREVIATIONS

ABC ATP binding cassette
ADM Adriamycin
ADR Alternative Dispute Resolution
AI Artificial intelligence
APL Acute promyelocytic leukaemia
ATG Autophagy-related gene
ATP Adenosine Triphosphate
BCRP Breast cancer-resistant protein
BNIP3 BCL2/adenovirus E1B 19 kDa protein-interacting protein 3
CQ Chloroquine
DNA Deoxy Ribonucleicacid
EAC Emergency Action Code
G. lucidum triterpene Ganoderma lucidum triterpene
IL-3 Interleukin-3
LRP Lung resistance protein
MCF-7 Michigan Cancer Foundation 7
MDR Multidrug resistance
MDR1 Multidrug resistance 1
MIPP 3-(2-methyl-1H-indol-3yl)-1-(4-pyridinyl)-2-propen-1-one
MLKL Mixed-lineage kinase domain-like protein
mRNA Messanger Ribonucleic Acid
MRP Multidrug resistance-associated protein
mTOR Mammalian target rapamycin
NCI National Cancer Institute
PCD Programmed cell death
PCR Ploymerase Chain Reaction
P-gp P-glycoprotein
RIP1 Receptor-Interacting Protein 1
RIP3 Receptor-Interacting Protein 3
RIPK1 Receptor-Interacting Protein Kinase 1
ROS Reactive Oxygen Species
shRNA Short hairpin RNA
TME Tumour microenvironment
UCP-2 Uncoupling protein 2
WHO World Health Organisation

Chapter 10
Marine Fungal Metabolites: A Future Therapeutic Drug Against Breast and Cervical Cancer – Alternative Medicine

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ABSTRACT

Fungi from marine environments are promising sources of therapeutics against cancer due to the production of various metabolites which contribute against the cancer cell growth and development. Various marine fungal metabolites have been studied against breast and cervical cancer which are the most common causes of death in women. Scopararane I from marine sediment fungi Eutypella sp. FS46 showed better activity against MCF 7. Alterporriol L from marine fungus Alternaria sp. induced cancer cell apoptosis by altering the reactive oxygen species and mitochondrial membrane potential. Apoptosis-inducing metabolite NMKD7 from marine sponge fungal symbiont Monascus sp. reported significant anticancer activity against breast cancer. Neoechinulin A and physcion produced by Microsporum sp. exhibited anticancer activity against cervical cancer by altering expressions of p53, caspase-9, etc. This review gives insight about the various marine fungal metabolites with potential anticancer activity against cervical and breast cancer and evidences it as a promising source of anticancer therapeutics.

INTRODUCTION

Cancer is a deadly disease that is the world's second largest cause of death. Cancer develops when any type of cell in the body fails to undergo apoptosis. Cancer cells proliferate in an aberrant, uncontrollable manner because they are not regulated by the signals that control normal cell function. As a result, there are over 120 different forms of cancer dependent on their site. A benign tumour can be surgically removed, but a malignant tumour has the immense complexity of spreading to other normal tissues, making treat-

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ment difficult. A genetic mutation can lead to the development of cancer. This cell-to-cell proliferation leads to tumour progression, which includes a slew of mutations that strengthen the malignant features of the tumour like uncontrolled growth. When these cells grow in size and become benign malignant, they migrate through connective tissue to blood and lymphatic cells, eventually spreading throughout the body (Cooper & Hausman, 2000).

In every country, cancer is a primary cause of death and a significant impediment to extending life expectancy. The rise of cancer as a leading cause of death is partly due to significant reductions in the mortality rates of stroke and coronary heart disease in comparison to cancer in many nations (Sung et al., 2021). Cancer is one of the leading causes of morbidity and mortality around the world, and it is anticipated to increase by 70% in the next two decades. Every year, about 8.8 million people are projected to die of cancer (Srinivasan et al., 2020). Cancer rates are continuing to rise as a result of rising global warming, malnutrition, and many environmental issues. According to the American Cancer Society, by 2050, the worldwide burden of cancer would have increased to 27 million new cases and 17.5 million cancer deaths due to population growth and ageing. Synthetic pharmaceutical formulations like chemotherapy create a variety of adverse effects in humans like neutropenia, blood clots, long term side effects and can even lead to death. So, there is a need for alternative anticancer therapeutics. Natural derivatives play a vital role in preventing cancer. Marine microorganisms and the metabolites produced by them are a significant source of anticancer drugs, although they haven't been extensively researched (Sithranga Boopathy & Kathiresan, 2010).

BREAST CANCER

With an expected 2.3 million new cases in 2020, female breast cancer has surpassed lung cancer as the main cause of global cancer incidence, accounting for 11.7 percent of all cancer cases. With 685,000 deaths worldwide, it is the fifth leading cause of cancer death. Breast cancer affects one out of every four women and is associated with one out of every six cancer fatalities. In the vast majority of countries, breast cancer ranks first in incidence and mortality (Sung et al., 2021). With advancement in molecular techniques like sequencing, gene expression studies of breast cancer have increased. This resulted in the molecular classification of breast cancer into six subtypes based on the expression of estrogen receptor, progesterone receptor, estrogen associated genes and genes associated with stimulation of proliferation like HER2. The six subtypes are ER+ tumors namely luminal A and luminal B, HER2 overexpressed tumours, triple negative breast cancer which does not express the foresaid genes, claudin low breast cancer and normal like breast cancer which resembles normal non-cancerous tissue in gene expression. Treatment for breast cancer depends on the type, but general treatment includes endocrine therapy, targeted therapy and chemotherapy (Luque-Bolivar et al., 2020).

CERVICAL CANCER

Another most common cancer in women is cervical cancer. With an estimate of 604,000 new cases and 342,000 deaths worldwide in 2020, cervical cancer is the fourth most commonly diagnosed cancer and the fourth major cause of cancer death in women (Sung et al., 2021). It arises from a succession of epithelial alterations known as cervical intraepithelial neoplasia (CIN). At cancer in situ, the biologi-

cal and genetic properties of the cells are irrevocably altered, and abnormal cells have the potential to spread to other anatomical sites. The main cause of cervical cancer is infection with the human papillomavirus (HPV), which is transmitted sexually. HPV infection is an essential but not sufficient factor in the development of cervical cancer. Invasive cervical cancer is frequently linked to certain types of high-risk human papillomavirus. HPV 16 and 18 are the carcinogenic strains that cause 70 percent of cervical cancer and roughly half of CIN 3 (Šarenac & Mikov, 2019).

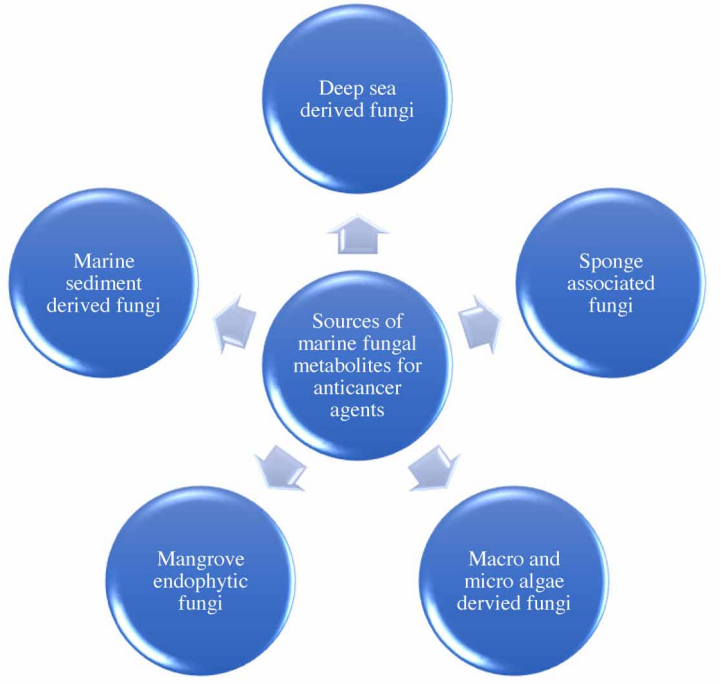
MARINE FUNGAL METABOLITES AND ANTICANCER ACTIVITY

More than half of all drugs are based on bioactive natural compounds, including approximately 80% of approved chemotherapeutic treatments. Natural products are used in the treatment of 87 percent of human ailments, including cancer. Natural bioactive compounds have cytotoxic effects because they target macromolecules expressed by cancer cells, such as those found in oncogenic signal transduction pathways. In vitro, in vivo (in mouse) models, and cancer clinical trials, a substantial number of marine-derived metabolites serve as anticancer agents by inhibiting the proliferation of human tumour cells. A new generation of anticancer therapeutics has been discovered thanks to advanced technology and extensive research on marine natural resources. They are currently being tested in clinical trials. Marine organisms have a lot of potential for discovering novel entities that can help with cancer prevention and treatment. Marine first appeared in the late 1800s. Following 1980, biotechnology evolved as a discipline that paved the direction to marine research, with applications such as drug development in focus. This research is still going on, and it's using advanced technology. About 22,000 microbial metabolites have been produced by marine microbes of which fungi accounts for 20% (Khalifa et al., 2019).

Marine microorganisms have proven to be a valuable source for developing novel compounds with a variety of biological capabilities. Marine microorganisms have evolved a variety of secondary metabolites with various bioactivities in response to the harsh environmental conditions of marine habitats and the presence of a variety of diseases and opportunistic microbes (Riera-Romo et al., 2020). Marine microbes like bacteria and fungi have attracted researchers' curiosity as potential new sources of physiologically active compounds. They exist in close proximity to soft-bodied marine animals that lack evident structural defence mechanisms, relying instead on chemical defence in the form of bioactive secondary metabolites produced by themselves or related microflora to survive in their harsh environment (Debbab et al., 2010).

Due to their ability to produce different enzymes and antibacterial compounds, fungi have a wide range of medical applications. Fungi, it has been discovered, to produce more antibacterial and anticancer compounds than bacteria. The efficiencies and functionalities of the active substances produced, on the other hand, are determined by the genes that cluster together in a genetic package known as biosynthetic gene clusters (BCGs). Marine fungi can be derived from a variety of sources like deep sea, algae, marine animals like sponge, mangroves etc. (Fig.1). Marine fungi are a rich source of bioactive molecules and have produced a diverse spectrum of anticancer agents (Noman et al., 2021). Several marine fungi have been reported to produce metabolites associated with cytotoxic and growth inhibitory anticancer activity (Saeed et al., 2021) against a variety of cancers which is listed in table 1. Fungi can be found in abundance in the marine environment, which includes water, sediments, crustaceans, driftwood, and marine mammals. According to recent investigations, there are about 10,000 marine fungus species, including those belonging to the phyla Ascomycota and Basidiomycota. Anticancer, antiviral, and antibiotic secondary bioactive components of marine natural products (MNPs) synthesized by fungi can

Figure 1. Various sources of marine fungal metabolites that have potential of anticancer activity



be found in the marine environment. Secondary metabolites are produced by organisms in the marine environment (SMs). These secondary compounds have distinct chemical structures and have a high potential as new medicines. More than 2225 bioactive compounds derived from marine species were shown to have anticancer properties. According to reports, polysaccharides, polyphenols and alkaloids are among the most powerful, biologically potent, and prevalent anticancer substances derived from marine creatures (Noman et al., 2021).

Marine fungi are a rich source of secondary metabolites that can be used in drug development. Despite the fact that marine fungus has been less studied than their terrestrial varieties, several relevant findings have been produced from a drug development aspect, highlighting their value in natural product discovery, which provided a variety of antimicrobial and anticancer agents. Marine fungi have produced unique chemical skeletons that might be exploited to develop medications of clinical value, beginning with the well-known example of cephalosporins (Deshmukh et al., 2018). Marine fungi have reported a wide variety of metabolites that are not found in terrestrial fungi (Srinivasan et al., 2020). In recent years, several classes of chemically unique metabolites from marine fungi have been identified, each with a diverse set of actions against various targets. Over a thousand metabolites from marine fungi have been shown to have therapeutic development potential, with several being anticancer compounds (Deshmukh et al., 2018).

Many pharmaceutically active anti-cancer leading proteins have been isolated from marine derived basidiomycetes, endophytic, and filamentous fungi, including *Leptosphaerinm Lignicolous, Leptosphaerodione* and others. Marine fungal metabolite Acremonin A was produced by *Acremonium* spp., and a xanthone derivative was produced by *Wardomyces anomalus*, both of which have anti-cancer activities against various cancer like colorectal, prostate, human chondrosarcoma cells, breast cancer,

Table 1. Marine Fungi associated with anticancer activity

SOURCE	FUNGI
Deep-sea	*Simplicillium obclavatum, Acaromyces ingoldii, Acrostalagmus luteoalbus, Paecilomyces lilacinus, Aspergillus sp., and Penicillium sp.*
Algae	*Paecilomyces variotii, Microsporum sp., and Aspergillus sp.*
Mangrove endophytic fungi	*Pestalotiopsis microspore, Campylocarpon sp. Stemphylium globuliferum, Bionectria ochroleuca, Pestalotiopsis clavispora, Mucor irregularis, Rhytidhysteron rufulum, Acremonium strictum, Penicillium sp, Lasiodiplodia sp., Fusarium sp., Dothiorella sp., Phomopsis sp., and Nigrospora sp.*
Marine Sediment-Derived Fungi	*Neosartorya fischeri, Eutypella scoparia, Eutypella sp., Aspergillus sp., Penicillium sp., and Aspergillus sp.*
Sponge associate fungi	*Arthrinium arundinis, Neosartorya laciniosa, Aspergillus sp., and Stachylidium sp.*

hepatocarcinoma and HeLa cells (Noman et al., 2021). Apralactone A, a novel macrolide obtained from the extract of marine fungi *Curvularia* sp. isolated from marine red algae *Acanthophora spicifera* was tested against a wide variety of cancer cell lines including 14 different solid tumour types and moderate activity was observed. One of the metabolite, (+)-(10E,15R)- 10,11-dehydrocurvularin was the most active, reported concentration dependent cytotoxic activity against nine tumours out of 36 cell lines tested and exhibited 25% selectivity (Noman et al., 2021). A compound called Aspergiolide-A was isolated from *Aspergillus glaucus*, a marine filamentous fungus showing cytotoxicity against a variety of cancer cell lines (Srinivasan et al., 2020).

Mangrove endophytic fungus *Halorosellinia* sp. derived metabolite anthraquinone SZ-685C suppressed the proliferation of various cancer cell lines like human breast cancer, prostate cancer, glioma and hepatoma (Hasan et al., 2015). Similarly, geodin isolated from soft coral *Sinularia* sp. associated marine fungus *Aspergillus* sp. exhibited anticancer activity against 6 different cancer cell lines namely, lung (NCI-H460, H-1975, A549), Breast (BT474), chronic myelogenous leukaemia cells (K562) and Prostate (DU1455) cells (Orfali et al., 2021). Various marine fungi have produced a metabolite called Sansalvamide A which is structurally unique cyclic depsipeptide. The cytotoxic assay revealed it was cytotoxic against a variety of cancer like colon, pancreatic, prostate, melanoma and breast cancer cells. It is reported that Sansalvamide A binds to N middle domain oof heat shock protein HSP90 and inhibited the formation of complex that is required for the growth of tumour cells (Khalifa et al., 2019).

MARINE FUNGAL METABOLITES AGAINST BREAST CANCER

Several secondary metabolites isolated from various marine sources have been studied for their potential cytotoxic and growth inhibitory activity against breast cancer. Secondary metabolite Alterporriol L which is a bioanthraquinone derivative isolated from marine fungus *Alternaria* sp. ZJ9-6B was reported to exhibit anticancer activity against breast cancer. On analysis of results of MTT assay, it was observed that alterporriol L induced cancer cell apoptosis and necrosis by increasing the ROS level which was studied using flow cytometry, reducing mitochondrial membrane potential and increasing the intracellular

free calcium ion levels (Huang et al., 2012). seven Pimarane type diterpene metabolites isolated from *Eutypella sp.* FS46 was evaluated for their anticancer activity against the MCF-7 breast cancer cell line in which scopararanes I showed better anticancer activity (Liu et al., 2017). Isosclerone, a metabolite isolated from marine derived fungus *Aspergillus fumigatus* was studied for their cytotoxicity against MCF-7 breast cancer cell line at a concentration of 60μM by MTT assay. The anticancer mechanism was further studied by analysing the gene and protein expression levels of matrix metalloproteases 2 to 9. This study showed that Isosclerone was capable of inhibiting MMP 2-9 by attenuating MAPK signalling pathway molecules in a dose dependent manner. Further, it also increased the expression of the tumour suppressor gene p53 and inhibited the cancer proliferation. A similar mechanism was observed with fumigaclavin C isolated from *A.fumigatus* and in addition to these mechanisms, fumigaclavin C also down-regulated NF-kappa B cell survival pathway as an anticancer mechanism (Li et al., 2013, 2014).

Meleagrin, a metabolite isolated from *Emericella dentata* Nq45 marine fungus was reported to inhibit the growth of the human breast cancer cell lines and was proposed as a potential metabolite against c-Metdependent metastatic and invasive breast malignancies (Mady et al., 2016). Cyclo(L-leucyl-L-prolyl), a marine fungal metabolite was reported to induce cytotoxicity and reduce the cell viability in triple negative breast cancer in the study using MDA-B-231 and MDA-MB- 468 TNBC cell lines but the cytotoxic activity was not observed in healthy normal breast cancer cell line MCF-12A. It suggested that this metabolite is cytotoxic only in cancer cells. The potential mechanism for the cytotoxic activity was studied to be inhibition of cell proliferation, cell cycle and migration. DNA damage like double stranded breaks was also observed leading to cell death and also interfering cell cycle of TNBC cell line through EGFR and CD151 signalling thus inhibiting cancer cell proliferation (Deepak et al., 2020). Weak cytotoxic activity against MCF- breast cancer cell lines were exhibited by the marine fungal metabolites like nigerapyrones B, D, E and asnipyrone A isolated from marine-derived fungi *Aspergillus niger* MA-132 (Chen et al., 2016). Mitoxanthrone-resistance in MCF Adriamycin resistant cell lines was reversed by the treatment with the marine fungal metabolite called Tryprostatin A isolated from *Aspergillus fumigatus* BM939. Similarly, Terrein isolated from *Aspergillus terrus* (PF-26 and PT06-2) and also from *Emericella variecolor* reported 100 fold cytotoxic activity than paclitaxel (chemotherapeutic drug) against MCF-7 cell line (Cherigo et al., 2015).

1403P-3, an anthracenedione derivative isolated from a fungal secondary metabolite isolated from the South China sea was tested for their cytotoxic effect against breast cancer cell line MDA-MB-435 and MCF-7 with IC_{50} values of 7.6 and 9.5 μM respectively. The mechanism behind the anticancer activity was elucidated by Annexin V-FITC/PI staining and western blotting and it was observed that 1403P-3 induced apoptosis in breast cancer cells by blocking the Akt activation, elevating caspase 8 and 9 and cleavage of PARP (Yuan et al., 2011). Metabolite isolated from *Hypoxylon rubiginosum* FS521 and cytochalasin P1 from *Xylaria* sp. SOF11 from the South China sea reported potential cytotoxic activity against the MCF-7 cell line. Similarly, out of 11 compounds isolated from *Penicillium brevicompactum* OUCMDZ-4920 from the South China sea, mycophenolic acid exhibited potential cytotoxicity against the MCF7 cell line. Many marine fungal metabolites like Coniochaetone J from *Penicillium* sp. SCSIO Ind16F01 and Asperienes A–D from *Aspergillus flavus* CF13-11 reported cytotoxic activity against the MCF-7 cell line (Yurchenko et al., 2021). Ophiobolin O produced by *Aspergillus ustus 094102,* a marine derived fungus was reported as pro-apoptotic in the MCF-7 cell line. It altered various signalling pathways like JNK, p38 MAPK associated with apoptosis. It also suppressed tumour formation in xenograft mouse models and was also associated with the reversal of Adriamycin resistance in breast cancer. Hirsutanol A, a marine fungal metabolite reported anticancer activity against MCF-7 by vari-

ous mechanisms like inhibition of cell proliferation, the elevation of reactive oxygen species level and induction of apoptosis (Gomes et al., 2015).

Fungal metabolites like anthraquinone and cinnamic acid obtained from marine endophytic fungi *Penicillium chrysogenum* was studied for their anticancer potential against human breast cancer cell line MCF-7. Ethyl acetate extract of the fungi was used for the identification of metabolites using GC-MS and evaluation of the anticancer activity. The anticancer activity was due to the membrane damage caused by the fungal metabolites which lead to the apoptosis of the cancer cells. The membrane damage in breast cancer cells by the fungal metabolites was identified on flow cytometry analysis (Parthasarathy et al., 2020).

Marine-derived fungus can be isolated from various sources like the deep sea, sea sediment, marine algae, marine animals and marine mangroves. Few marine fungal metabolites that exhibited anticancer activity against breast cancer are listed in table 2.

DEEP-SEA ASSOCIATED FUNGAL METABOLITES AGAINST BREAST CANCER

Acaromycin A and (+)-cryptosporin were isolated from the deep-sea (South sea in China) derived fungus *Acaromyces ingoldii FS121*. These compounds were isolated by the techniques like fermentation and a series of chromatographic separation and its structure was elucidated using one and two dimensional NMR, Mass spectroscopic and circular dichroism techniques. Both the compounds reported growth inhibition activity against the MCF7 cell line. Secondary metabolites like ergosterol peroxide derivative, ergosterol peroxide and cerebroside AD were isolated from deep-sea fungus *Paecilomyces lilacinus* ZBY-1 and cytotoxic activity against breast cancer cell lineMCF7 was observed. Deep-sea fungal metabolites like luteoalbusins A–B and gliocladines C–D isolated from fungus *Acrostalagmus luteoalbus* SCSIO F457 and Breviones I and A isolated from *Penicillium* sp. showed significant anticancer activity against MCF7 breast cancer cell lines (Deshmukh et al., 2018).

MARINE SEDIMENT-ASSOCIATED FUNGAL METABOLITES AGAINST BREAST CANCER

Marine fungi *Penicillium* sp. ArCSPf was isolated from the continental slope of the Eastern Arabian Sea. LC-MS/MS analysis of Ethyl acetate extract of Penicillium sp. ArCSPf ethyl acetate extract revealed the secondary metabolite (Z)-Octadec-9-enamide which was associated with potential anticancer activity against MCF-7 Breast cancer cells. Anticancer activity was confirmed by microscopic analysis which revealed cell shrinkage, loss of membrane integration and detached cells (Farha & Hatha, 2019). Around 10 metabolites were isolated from Vietnamese marine sediment derived fungo *Aspergillus flocculosus* and structural analysis was carried out using NMR and Mass Spectrometry techniques. Their cytotoxicity against breast cancer cell line MCF-7 was evaluated. In the cytotoxicity assay, Insulicolide A, showed better anticancer activity against breast cancer (Yurchenko et al., 2019). *Aspergillus versicolor* (MST-MF495) which is a common terrestrial isolate was isolated from a marine source of beach sand sample from Cottesloe at low tide region. The metabolite cotteslosins A isolated showed weak cytotoxic activity against breast cancer cell line with EC50 at 148.03mM (Debbab et al., 2010).

Spectroscopic, mass spectrometric and NMR analysis of metabolite derived from marine derived fungus *Aspergillus* sp. SCSIO F063 obtained from a marine sediment sample in China revealed that the metabolite is chloroaveratin derivative. Chloroaveratin exhibited inhibitory activity against the breast cancer cell line MCF-7 with an IC50 value of 6.6 μM. Scopararane D, libertellenone A and diaporthein B produced by marine derived fungus *Eutypella scoparia* FS26 isolated from marine sediment soil sample from South China sea were evaluated for their anticancer activity against MCF7 cell line using MTT assay. Mild and potent antiproliferative activity against MCF-7 cell line was reported by Scopararane D and libertellenone A, diaportheinB respectively (Deshmukh et al., 2018).

MARINE ANIMALS ASSOCIATED FUNGAL METABOLITES AGAINST BREAST CANCER

Out of twenty three marine fungi isolated from sixteen different sponges in the Gulf of Mannar region, *Monascus sp.* NMK7 associated with marine sponge *Clathria frondifera* reported significant anticancer activity against breast cancer cell lines namely MCF-7, T47D, MDA-MB-231, MDA-MB-468 and MCF-10A. Column chromatography and HPLC analysis reported the fungal metabolite monacolin X as the metabolite associated with anticancer activity inducing cell death. Chromatin analysis revealed that anticancer activity was due to nuclear damage caused by reactive oxygen species, which also disrupts the mitochondrial membrane and leads to apoptosis (Nagabhishek & Madankumar, 2019). Crude extract of marine fungi *Eurotium cristatum* associated with *Mycale* sp. marine sponge was tested for their anticancer activity against MCF-7 breast cancer cell line and significant cytotoxic activity was reported. Further, NMR spectral analysis revealed the presence of 2-(2', 3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl) benzaldehyde which showed better anticancer activity than other two other metabolites identified and the anticancer mechanism was by arresting the cell cycle at the G1 phase with a corresponding decrease of cells in S and G2/M phase. So, suggested it as a potential anticancer agent against breast cancer (Almeida et al., 2010).

Preussin, a hydroxyl pyrrolidine derivative was isolated from fungus *Aspergillus candidus* KUFA 0062 which is associated with marine sponge *Epipolasis sp.* Its antiproliferative and cytotoxic activity against breast cancer cell lines namely MCF-7, SKBR3 and MDA-MB-231 were analysed in both 2D and 3D cultures and significant cytotoxic and anti-proliferative activity was observed. Caspase 3 immunostaining and cell morphology analysis using electron microscopy also confirmed the reduction in cell viability of the breast cancer cell lines treated with preussin (Malhão et al., 2019). *Penicillium oxalicum* SCSGAF 0023 isolated from marine gorgonian produced the metabolite called oxalicumone E and A which showed significant cytotoxic activity against eight cell lines including MCF7 (Deshmukh et al., 2018).

MARINE ALGAE ASSOCIATED FUNGAL METABOLITES AGAINST BREAST CANCER

Aspergillus isolated from marine algae from the Konkan coast exhibited significant anticancer activity against cervical cancer cell line (HeLa), Breast cancer (MCF-7), lung cancer (A549) and skin cancer (A431) cell lines analysed by MTT and resazurin assay. GC-MS analysis of the Aspergillus unguis crude extract revealed the presence of a variety of secondary metabolites like azelaic acid, azetidine,

Table 2. Various marine derived fungal metabolites exhibiting anticancer activity against breast cancer

SOURCE	FUNGUS	METABOLITE	CELL LINE TESTED	EFFECT
Marine	*Aspergillus fumigatus*	Isosclerone	MCF-7	Cytotoxicity
Marine	*Aspergillus terrus, Emericella variecolor*	Terrein	MCF-7	Cytotoxicity 100 fold than Paclitaxel
Marine	*Aspergillus fumigatus* BM939	Tryprostatin A	MCF Adriamycin resistant cell lines	Reversal of mitoxanthrone-resistance in breast cancer
Deep-sea	*Acaromyces ingoldii FS121*	Acaromycin A and (+)-cryptosporin	MCF-7	Growth inhibition
Marine sediment	*Aspergillus flocculosus*	Insulicolide A	MCF-7	Anticancer activity
Marine sponge *Clathria frondifera*	*Monascus sp.* NMK7	monacolin X	MCF-7, T47D, MDA-MB-231, MDA-MB-468 and MCF-10A	Cytotoxicity due to nuclear damage
Marine gorgonian	*Penicillium oxalicum* SCSGAF 0023	oxalicumone E and A	MCF-7	Cytotoxicity
brown alga *Pelvetia caniculat*	*Paradendryphiella salina* PC 362H	(-)-hyalodendrin	MCF-7	Cytotoxicity
Mangrove	*Aspergillus tubingensis* (GX1-5E)	naphtho-γ-pyrones	MCF-7 and MDA-MB-435	Anticancer activity
Marine mangrove *Acanthus ilicifolius*	*Diaporthe phaseolorum* SKS019	5-deoxybostrycoidin	MDA-MB-435	Anticancer activity

furopyrans which were associated with the observed anticancer activity. Possible anticancer mechanisms were identified as G1 phase cell cycle arrest, reactive oxygen species (ROS) dependent mitochondrial membrane potential loss and further leading to apoptosis (Kamat, Kumari, Taritla, et al., 2020).

(-)-hyalodendrin isolated from *Paradendryphiella salina* PC 362H marine fungal strain from brown alga *Pelvetia caniculat* exhibited potent antitumour activity against MCF7 epithelial cancer cell line and invasive stem cell like cancer cell line MCF7-Sh-WISP2 counterpart. (-)-hyalodendrin treatment caused anticancer activity by the mechanism like inducing changes in phosphorylation of p53 and alteration in the expression of HSP40, HSP 60 and HSP70 (Dezaire et al., 2020). In brine shrimp assay, epiepoxydon isolated from marine endophyte, *Apiospora montagnei* of the North Sea alga *Polysiphonia violacea* reported significant cytotoxic activity against MCF7 breast adenocarcinoma cell line with LC50 value of 3.6 mg/mL(Nagabhishek & Madankumar, 2019). Ethyl acetate extract of *Chartomium globosum* associated with green alga *Chaetomorpha media* from Konkan coastline was studied for their Cytotoxic activity against MCF-7 breast cancer cell line. Gas Chromatography-Mass Spectrometry analysis was carried out to find the metabolite associated with the anticancer activity and it revealed the metabolite Chrysin, a dihydroxyflavone. The anticancer activity was due to the apoptosis caused by G1 phase cell cycle arrest, mitochondrial membrane potential loss and Reactive Oxygen species production (Kamat, Kumari, Sajna, et al., 2020).

MARINE MANGROVE ASSOCIATED FUNGAL METABOLITES AGAINST BREAST CANCER

The endophytic fungi associated with mangroves are the second-largest ecological class of marine fungi and could be used to isolate new bioactive chemicals. Because of their importance in ecology, they have attracted researchers. Only a few types of mangrove fungi have been examined so far (Uzma et al., 2018). SZ-685C, an anthracycline analogue is a metabolite isolated from a marine derived mangrove endophytic fungi. Anticancer activity of SZ-685C was reported in MTT assay and it was further analysed to identify the possible anticancer mechanism. SZ-685C was observed to suppress the proliferation and growth of breast cancer in both in-vitro and in vivo studies (Xenograft mouse model). Anticancer activity was due to both intrinsic and extrinsic pathways of apoptosis by down-regulation of the Akt pathway and upregulation of FOXO pathway and SZ-685C was reported as a potential anticancer metabolite against breast cancer by acting as Akt pathway inhibitor (Xie et al., 2010).

Another study reported that marine fungal metabolite 1386A isolated from the mangrove fungus in the South China Sea possessed anticancer activity against breast cancer cell line and it alters the miRNA profiles of MCF-7 causing apoptosis (Tang et al., 2012). Cytotoxic activity against MCF-7 and MDA-MB-435 cell line was reported by naphtho-γ-pyrones isolated from mangrove endophytic fungi *Aspergillus tubingensis* (GX1-5E) (Chen et al., 2016). Merulin A and C, sesquiterpene metabolites produced by endophytic fungus XG8D (Basidiomycete) isolated from *Xylocarpus granatum* showed significant anticancer activity against breast cancer cell line with IC50 value of 4.98 μg/mL. Out of five oxygenated chromones produced by endophytic fungus *Rhytidhysteron rufulum* BG2-Y isolated from healthy leaves of mangrove plant *Bruguiera gymnorrhiza* in Thailand Pak Nam Pran, two metabolites namely hytidchromones A and C showed significant anticancer activity against MCF7 cell line with IC50 values of 19.3 and 17.7 μM respectively (Uzma et al., 2018). Endophytic fungi *Lasiodiplodia theobromae* ZJ-HQ1 isolated from the leaf of marine mangrove *Acanthus ilicifolius* from China produced the metabolites chloropreussomerins A and B, spreussomerin, preussomerin G, H and F. All these metabolites exhibited significant cytotoxic activity against MCF7 cell lines (Deshmukh et al., 2018).

Similarly, *Diaporthe phaseolorum* SKS019, an endophytic fungus isolated from *A.ilicifolius L.* on phytochemical screening revealed the compound 5-deoxybostrycoidin. On cytotoxicity analysis against MDA-MB-435, 5-deoxybostrycoidin showed potential anticancer activity with an IC50 value of 5.32 μM (Jeewon et al., 2019). Structure of Ethyl-2,4-dihydroxy-6-(8′ - hydroxynonyl)- benzoate isolated from mangrove endophytic fungi *Lasiodiplodia* was studied using spectroscopic techniques. On analysis of their cytotoxic activity, it showed significant anticancer activity against breast cancer cell line MCDA-MB-435 with IC50 value 10.1μM. Inhibitory activity against the MCF-7 cell line was exhibited by two metabolites isolated from mangrove derived fungus *Aspergillus terreus* (No. GX7-3B) and its structure was elucidated using spectroscopic data. quinone derivative metabolite derived from *Nigrospora* sp. MA75, an endophytic fungus isolated from marine semi-mangrove plant *Pongamia pinnata* exhibited potent growth inhibition of MCF-7 tumour cell line with an IC50 value of 4 μg/mL and its structural characteristics were studied using spectroscopic analysis. Similarly, anthraquinone Deoxybostrycin derived from *Nigrospora* sp. No.1403 showed anticancer activity against MDA-MB-435 cell line with an IC50 value of 3.1 μM (Deshmukh et al., 2018).

MARINE FUNGAL METABOLITES AGAINST CERVICAL CANCER:

Several marine fungal metabolites have been studied for their potential anticancer activity against cervical cancer. Anthraquinone derivative physicon was isolated from the culture broth extract of marine derived fungus, *Microsporum sp.* Its cytotoxic effect against cervical cancer cell line (HeLa) was studied changes in expression of p53, p21, down-regulating Bcl-2, upregulating Bax and activating Caspase-3,9 proteins. In addition, other mechanisms like an increase in Reactive Oxygen Species level was also observed in the HeLa cell line indicating anticancer activity against cervical cancer (Wijesekara et al., 2014). Meleagrin, a metabolite isolated from *Emericella dentata* Nq45 marine fungus reported cytotoxic activity against human cervical cancer cell line KB-3-1 with an IC_{50} value of 3.07 μM. In addition to this, anticancer activity against the multidrug-resistant subclone KB-V1 cell line was also observed with an IC_{50} value of 6.07 μM (Hamed et al., 2020, p. 45). Iso-pencillixanthone A isolated from marine fungus *Penicillium oxalicum* reported anticancer activity against cervical vincristine resistant cell line HeLa/VCR by increasing the intracellular drug concentration via stimulating the P-gp ATPase activity and attenuating P-gp expression in resistant HeLa cell line. Other anticancer mechanisms were also observed including ROS activity was increased; Mitochondrial membrane potential was depolarized and cytochrome c release from mitochondria was promoted. Apoptosis was promoted by activating caspase 9, 3 and PARP. Similar efficacy was observed in the xenograft model of HeLa/VCR suggesting Iso-penicillixanthone A as a potential anticancer agent against vincristine resistant cervical cancer (Chen et al., 2018).

Neoechinulin A, a prenylated alkaloid isolated from marine derived fungus *Microsporum sp.* showed significant cytotoxic activity against the HeLa cell line and it was investigated based on the expression of p53, p21, Bcl-2, Caspase 9, 3 and Bax proteins. Apoptosis was induced by upregulation and down-regulation of Bax and Bcl-2 respectively and also by activating the caspase 3 pathway (Wijesekara et al., 2013). Gliotoxin, a secondary metabolite produced by marine fungus *Aspergillus sp.,* exhibited significant anticancer activity against cervical cancer cell lines HeLa. Gliotoxin activated the expression of caspase enzymes, downregulated Bcl-2 expression and cytochrome c was released inducing apoptosis in cells. Further other morphological changes like DNA fragmentation, chromatin condensation and mitochondrial membrane potential disruption was also observed indicating apoptosis and cytotoxicity. Thus, gliotoxin was reported as a significant anticancer metabolite against cervical cancer (Nguyen et al., 2014). Metabolites isolated from marine *Penicillium* sp. also exhibited potent cytotoxic activity against the HeLa cell line (Riera-Romo et al., 2020). Cytotoxicity against HeLa cell line was reported by Diorcinol D and E isolated from marine derived fungus *Aspergillus versicolor* (Deshmukh et al., 2018).

Penicimutide and chromosulfine isolated from a mutant strain of marine derived fungus *Penicillium purpurogenum* G59 which exhibited neomycin resistance reported significant anticancer activity against the HeLa cell line (Deshmukh et al., 2018). Significant cytotoxic activity against the HeLa cell line was reported by Alterperylenol produced by marine fungi from marine plants (Zhao et al., 2018). Similarly, anticancer activity against cervical cancer cell lines was reported for pestaloficiol J, K, and L isolated from fungal endophyte *Pestalotiopsis fici,* terphenylllin and prenylterphenyllin isolated from deep-sea-derived fungus *Aspergillus candidus* and various prenylterphenyllins and prenylcandidusins isolated from the endophytic fungus *Aspergillus candidus* LDJ-5 (Jeewon et al., 2019; Orfali et al., 2021). Campyridone D and ilicicolin H isolated from a fungus isolated from mangrove plant *Sonneratia caseolaris* (root) exhibited cytotoxic activity against HeLa cell line with IC50 values 8.8 and 4.7 μM respectively (Deshmukh et al., 2018). Fungal metabolites from various marine derived sources that exhibit anticancer activity against cervical cancer have been listed in table 3.

Table 3. Various marine derived fungal metabolites exhibiting anticancer activity against Cervical cancer

SOURCE	FUNGUS	METABOLITE	CELL LINE TESTED	EFFECT
Marine	*Microsporum sp*	physicon	HeLa	Cytotoxicity by ROS production
Marine	*Penicillium oxalicum*	pencillixanthone A	vincristine resistant cell line HeLa/VCR, xenograft model of HeLa/VCR	Anticancer activity in vincristine resistant cells
Marine plants		Alterperylenol	HeLa	Anticancer activity
Marine Sediment	*Trichoderma sp.*	Trichoderone	HeLa	Cytotoxicity
Alkaline saline soil from Laizhou Bay	*Penicillium* sp. SXH-65	Arisugacin B and Arisugacin F	HeLa	Cytotoxicity
Marine algae *Sargassum muticum*	*Aspergillus sp*	quinoline, indole, 2,4-bis (1,1- dimethyl) phenol and hexadecenoic acid	HeLa	Cytotoxicity

MARINE SEDIMENT-ASSOCIATED FUNGAL METABOLITES AGAINST CERVICAL CANCER

On bioactivity guided fractionation and purification of crude extract of *Trichoderma sp.* isolated from China Sea sediment revealed the presence of two major metabolites. Out of the two, trichoderone metabolites showed effective anticancer activity against MCF-7 and MDA-MB-435s breast cancer cell line and HeLa cervical cancer cell line with IC_{50} values of 63.5 μM, 617 μM and 85.6 μM respectively (You et al., 2010). Arisugacin B and Arisugacin F produced by *Penicillium* sp. SXH-65 isolated from alkaline saline soil from Laizhou Bay coast in China reported weak cytotoxicity against HeLa cell line with IC50 value ranging between 24 and 60 μM (Uzma et al., 2018). Nine C9 polyketides isolated from *Aspergillus* sp. in deep-sea sediment of the pacific ocean were structurally analysed using NMR, mass and CD spectroscopy techniques. They were identified as aspiketolactonol, aspilactonols A–F, aspyronol and epiaspinonediol. All the nine metabolites reported cytotoxic activity against the HeLa cell line. NMR and Mass spectrometry analysis revealed the metabolites penipacids A and E and its analogue from Fungus *Penicillium paneum* SD-44 isolated from marine sediment sample in the South China Sea. The analogue metabolite reported significant cytotoxic activity against the HeLa cell line with IC50 value better than the positive control (Deshmukh et al., 2018).

MARINE ALGAE ASSOCIATED FUNGAL METABOLITES AGAINST CERVICAL CANCER

Secondary metabolites isolated from seaweed endophytic marine fungus *Talaromyces purpureogenus* was revealed by Gas Chromatography-Mass Spectroscopy (GC-MS) analysis of fungal extract. It included various metabolites like 3-nitropropanoic acid, 4H-pyan-4-one 5-hydroxy-2-(hydroxymethyl), hexadecenoic acid and ocatdecanoic acid. On analysis of the cytotoxic activity of the metabolites against six different cell lines, the highest anticancer activity was observed against the HeLa cell line followed by

the MCF-7 cell line. The potential anticancer mechanism was reported as inducing membrane damage and mitochondrial depolarization causing apoptosis in HeLa cell lines. These metabolites were found to be specific in action as they didn't exhibit cytotoxicity to normal human embryonic kidney cell line (HEK293) (Kumari et al., 2018). Ethyl acetate extract of *Aspergillus sp*. isolated from *Sargassum muticum*, a marine brown alga was tested for its cytotoxic activity against the HeLa cell line which showed potent anticancer activity. GCMS analysis revealed the presence of metabolites like quinoline, indole, 2,4-bis (1,1- dimethyl) phenol and hexadecenoic acid which are associated with cytotoxic activity. A various anticancer mechanism like increase in production of ROS, mitochondrial membrane potential depolarization and caspase 3 pathway activation leading to intrinsic apoptotic pathway was observed and another apoptotic mechanism like cell cycle arrest at G2/M phase was also observed (Taritla et al., 2021). Cinnamolide derivative and insulicolide A produced by *Aspergillus ochraceus* Jcma 1F17 derived from marine algae exhibited significant anticancer activity against the HeLa cell line (Deshmukh et al., 2018).

CHALLENGES IN DEVELOPMENT OF FUNGAL METABOLITE BASED ANTICANCER DRUGS

Even though several studies have reported various anticancer compounds isolated from marine fungal based metabolites, a vast majority of ocean habitat including marine microbes, animals, algae, crustaceans and sediments remain underexplored due to few problems encountered like huge size and complexity in structure (with multiple chiral centres) of the marine metabolites and obstacles faced due to the lack of advanced technologies that aid in marine research. Despite these limitations, marine fungal metabolites serve as an important potential source of anticancer compounds especially against breast and cervical cancer. The development of advanced techniques in molecular biology, genomics, proteomics, metabolomics and bioengineering can help in the development and isolation of a variety of anticancer compounds from marine sources (Bhatnagar & Kim, 2010).

CONCLUSION

Quest for modern anticancer drugs is aiming at enhanced cytotoxic activity in terms of their efficacy, accuracy, target specificity and sensitivity of anticancer compounds. The marine environment especially fungal metabolites can serve as a rich source of such natural anticancer compounds. A vast number of marine derived fungal metabolites are potential sources of anticancer drugs not only against breast and cervical cancer but also against a variety of cancer cells. Further research with advanced technologies in marine fungal metabolite for anticancer drug development can produce a groundbreaking anticancer drug which will be a natural therapeutic, specific in its activity thus eliminating the side effects caused due to chemotherapeutic drugs. Marine fungal based metabolites paves way for a new array of future anticancer therapeutics, especially against cervical and breast cancer.

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Chapter 11
Medicinal Plants for the Treatment of Liver Cancer

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ABSTRACT

Liver cancer, which is fifth most common malignancy worldwide, is caused by drugs, chemicals, pollutants, and infections from parasites, etc. WHO estimates about three quarters of the world's population currently use herbs to cure various diseases, including liver cancer, which show that the medicinal plants have a very important place in the health of humans. Many experimental studies have been conducted to find the plants and their formulations for treatment of liver cancer. Many medicinal plants showed antiviral activity, antihepatotoxicity activity, stimulation of liver regeneration, and anticancer activity. Furthermore, many bioactive compounds in plants could protect the liver by antiproliferative activity. In this chapter, the authors review diverse medicinal plants and their bioactive compounds used in therapeutic and management intervention against liver cancer.

1. INTRODUCTION

The incidence of liver cancer (LC) ranks fifth in the world, with an estimation of 782,000 new deaths and 841,000 new cases of liver cancer that occurred around the world in 2018 (Bray et al., 2018). Moreover, liver cancer incidence and mortality are both increasing at a faster pace by almost 3% per year (Siegel et al., 2017). In developing countries, the incidence rate is two to three times that of developed countries (Bosch et al., 1999). The differences in the incidence of liver cancer between and within countries strongly indicate differences in exposure to risk factors. The role of chronic infection with hepatitis B virus and

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hepatitis C virus (HBV and HCV) in the etiology of liver cancer has been recognized. The attributable risk of liver cancer for each hepatotropic virus varies from country to country, but the combined impact of persistent HBV or HCV infection accounts for more than 80% of global liver cancer cases. Other documented risk factors, such as dietary exposure to aflatoxin, smoking, alcohol consumption, and oral contraceptives, can explain differences in residues between and within countries. The interaction between some risk factors has been assumed and is the subject of active research. Laboratory techniques and biomarkers, such as polymerase chain reaction testing of HBV DNA and HCV RNA, and specific mutations associated with exposure to aflatoxin, may help provide quantitative estimates of the risks associated with these factors (Bosch et al., 1999).

Hepatocellular carcinoma and intrahepatic cholangiocarcinoma are the two main forms of primary liver cancer. Hepatocellular carcinoma can damage liver cells through the production of oxidative stress and inflammation related to the occurrence of liver cancer (Kumar et al., 2011). Several types of chemotherapy drugs have been used to treat liver cancer, such as cisplatin, 5-fluorouracil, and paclitaxel. However, due to the reduction of multidrug resistance proteins and apoptosis proteins, these drugs usually have some problems. Recently, many medicinal plants have been studied as alternatives to chemotherapy drugs. Most medicinal plants derived from traditional medicines are safer than effective chemicals. This may be due to the traditional use of humans for generations. Only those that show the efficacy and safety of the treatment will be recorded and used until now (Manosroi et al., 2015).

2. MEDICINAL PLANTS USED FOR THE TREATMENT OF LIVER CANCER

Medicinal plants have been shown effective to inhibit the activity of agents that cause liver cancer with increased liver function. Many studies presented the effect of medicinal plant extracts on liver cancer and isolate and find out the bioactive compounds as potential drug candidates. There are so many compounds found including quercetin, luteolin, wogonin, baicalein, stigmasterol (Wu et al., 2020). They were isolated from medicinal plants such as *Artemisiaprinceps, Artemisia vulgaris, Amorphophallus campanulatus, Brucea javanica, Broussonetia luzonica, Dracocephalum kotschyi, Graptopetalum paraguayense, Petasites japonicas* (Nasreen et al., 2018). Below we summarize some medicinal plants and bioactive compounds that are used for the treatment of liver cancer.

2.1 Graptopetalum Paraguayense

Graptopetalum paraguayense (GP) belongs to the Crassulaceae family and has many health benefits. In Taiwan, GP is a commonly used herbal medicine. The stem extract of GP has antioxidant properties and the highest antioxidant activity. It is effective against human liver cancer (Hep G2) cell lines (Chen et al., 2008). In the liposome model system, the antioxidant capacity of the extracts, their ability to scavenge free radicals and their effects on Fe/ascorbic acid-induced lipid peroxidation were evaluated. In another study, the extract came from 30% DMSO GP (Hsu et al., 2015). HH-F3, which is rich in proanthocyanidins, partially inhibits the expression of AURKA and AURKB proteins, and disrupts the ability of cell cycle progression and the mitotic integrity of HCC. In addition, the anticancer effects of proanthocyanidins have been previously described (Neuwirt et al., 2008). These results demonstrate the antioxidant and anti-liver cancer potential of stems.

2.2 Petasites Japonicus

Petasites japonicus (PJ) is a plant of the Compositae family. Its roots and stems are used as traditional Chinese medicine in Japan and Korea to treat or prevent migraines and tension headaches. Sesquiterpenes, lignans and flavonoids are the components of PJ. PJ has anti-allergic, antioxidant activity, metabolic improvement, and neuroprotective effects (Hiemori-Kondo & Nutrition, 2020). *In vitro* and *in vivo*, the methanol extract of PJ root has been shown to have anti-proliferative effects on Hep3B hepatocellular carcinoma cells (Kim et al., 2015). The methanol extract of PJ decreased cell viability in a concentration-dependent manner. In addition, it was found that the methanol extract of PJ inhibits the growth of Hep3B HCC cells by inhibiting the Akt/mTOR and Wnt signaling pathways (Chen et al., 2018). These results indicate that the methanol extract of PJ has anti-cancer effects on Hep3B HCC cells.

2.3 *Broussonetia Luzonica* (Moraceae) Blanco

Broussonetia luzonica (Blanco) (Moraceae) (B. luzonica) (BL) is an endemic tree species in the Philippines, commonly found in shrubs and forests at low and medium altitudes. For Filipinos, especially those from northern Luzon, the leaves and flowers are edible and can be used to make vegetable recipes such as pinakbet and bulanglang (Snelder & Lasco, 2008). Compounds present in other species of Broussonetia exhibit significant biological activity. Gas chromatography-mass spectrometry showed the quantity (%) of the three main biologically active compounds in the ethyl acetate leaf extract. They are phytol (20.28%), 1,2,3-propanetriol, monoacetate (21.21%) and squalene (6.85%) (Casuga et al., 2016). BL showed effective anti-proliferative effects on estrogen receptor-positive MCF-7 breast cancer cells *in vitro* (Guo et al., 2013). In addition, its methanol extract is cytotoxic to HeLa cell line and HepG2 cell line (Kumar et al., 2014).

2.4 Brucea Javanica

The Chinese herbal medicine *Brucea javanica* (BJ) is effective and relatively safe and has been playing an important role in the treatment of patients in East Asia and its surrounding areas for many years. Recent reports indicate that this herb has a wide range of anti-tumor activities against various cancer cells. As an effective and relatively safe Chinese herbal medicine, the drug has cured patients with amoebic dysentery, malaria and various parasitic diseases in East Asia for many years (Nakao et al., 2009). The emulsified formula of BJ seeds has been approved and marketed in Eastern countries for the treatment of various types of cancer, such as the diagnosis of advanced lung cancer (Nie et al., 2012). Chemopreventive BJ fruit extract showed cytotoxic activity in pancreatic cancer cells (Lau et al., 2008). Combined with conventional chemotherapy, BJ targets is the intrinsic Epidermal Growth Factor Receptor (EGFR) of liver cancer cells and progenitor stem cell-like cells (Chen et al., 2016). The results of the study show that BJ is a promising complement to current treatment options and highlights the opportunity of BJ as a practical way to inhibit the growth of liver cancer stem cells.

2.5 Artemisia Princeps Var. Orientalis

Artemisia princeps var. *orientalis* (AP) is a well-known traditional herbal medicine in Asia and a plant belonging to the Asteraceae family. Bioactive constituents of AP have been investigated in several studies,

and some of them, such as flavonoids, glycosides, terpenoids, sterols, coumarins and polyacetylenes (Ryu et al., 1997). Previous studies have shown that these bioactive constituents have antimalarial, antiviral, antioxidant, and anticancer effects (Tan et al., 1998). Besides, the anticancer and antioxidant activity of AP extract in human hepatoma HepG2 and Hep3B cells has been proven (Choi & Kim, 2013). AP extract inhibited cell proliferation at concentrations lower than 100 μg/mL and the inhibition was less dose-dependent than time-dependent. HepG2 and Hep3B cells exposed to 5, 100, and 200 μg/mL AP for 72 h. Exposure to AP extract resulted in a decrease in the G2/M phase cell population and a significant increase in the number of cells in G1 phase. Moreover, AP extract induced p53 expression of HepG2 cells in a dose-dependent manner and played a role in upregulation of Bax in both HepG2 and Hep3B cells and the downregulation of Bcl-2. These results indicate the potential role of AP extract as an anti-cancerigen agent in hepatocarcinoma cell lines.

2.6 Dracocephalum Kotschyi

Dracocephalum kotschyi (DK) is a plant belonging to the Lamiaceae family and is found abundantly in southwest Asia. DK due to its antispasmodic and analgesic, anti-hyperlipidemia (Sajjadi et al., 1998) and immunomodulatory effects (Amirghofran et al., 2000). In addition, DK extract (250 μg/mL) only induces reactive oxygen species (ROS) formation, mitochondrial membrane permeabilization (MMP), mitochondrial swelling, and cytochrome c release in tumor hepatocytes but not non-tumor hepatocytes (Talari et al., 2014). These findings indicate that DK is a promising anti-cancer plant that acts on the mitochondria of liver cancer cells.

2.7 Allium Sativum

Allium sativum (AS), garlic, is a member of the Liliaceae family and is grown and consumed worldwide. The use of AS for medicinal purposes can be traced back to ancient times. AS has a powerful antioxidant defence system that can minimize intracellular oxidative stress (Banerjee et al., 2003). Among the various components of AS, organic sulfur compounds (OSCs) are considered to be the main biologically active components. Garlic oil (GO) contains more than 30 OSCs (Wu et al., 2001). Prove the *in vivo* chemoprotective effect of GO on NDEA-induced liver cancer (Zhang et al., 2012). This chemical protective effect of GO may be related to the enhancement of antioxidant activity and induction of cell apoptosis. Moreover, garlic powder and alliin-rich garlic extract inhibit the growth of human lymphoid leukemia cell lines in a dose-dependent manner, but only when used as a mixture can inhibit the growth of human liver cancer and human colorectal cancer cells. The anti-proliferative effect of AS is due to the decomposition products of alliin catalyzed by the alliinase system in garlic powder (Siegers et al., 1999). These findings may indicate the potential use of AS in the chemoprevention of hepatocellular carcinoma.

2.8 Curcuma Longa

Curcuma longa (CL) is a plant of the genus Turmeric in the ginger family. Many components of CL have been identified as having anti-inflammatory, anti-oxidative stress and anti-cancer properties (Jee et al., 1998; Quiles et al., 2002). Regarding the use of medicinal phytochemicals, the main bioactive components of CL are consistent with two parts: crystals and volatile oils. The crystalline part is usually obtained by alcohol extraction, which mainly contains these related curcumin: curcumin, bis-demethoxycurcumin

and demethoxycurcumin. Besides, the volatile fraction extracted by steam distillation contains a series of related sesquiterpenoids, including turmeric, β-elemene and germacrone (Zhou et al., 2007). In fact, other phytochemicals, especially sesquiterpenoids in turmeric oil, have been shown to have anticancer effects in some studies (Hastak et al., 1997). Recently, turmeric, the main sesquiterpene compound in turmeric oil, has been shown to have anti-inflammatory and anti-cancer effects. Curcumin can not only inhibit cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS), but also induce apoptosis in various cancer cell lines (Ji et al., 2004). In addition, turmeric shows immunomodulatory activity that may contribute to anti-cancer effects (Yue et al., 2010). In conclusion, turmeric oil has shown promising properties in liver protection, HCC chemoprevention, and cancer patients as a long-term maintenance drug to prevent tumor recurrence.

2.9 Saffaron

Saffron, the dried stigmas of Crocus sativus flowers, belongs to the class Liliatae (monocotyledons), sub-class Liliidae, order Liliales, Iridaceae family and genus Crocus. In fact, *Saffron* has biologically useful properties. *Saffron* extract and biologically active compounds of *Saffron*, including crocetin, crocin, carotene, and safranal, have been shown both *in vitro* and *in vivo* to possess anti-inflammatory, antioxidant, anticancer, and memory-improving properties (Abdullaev & Espinosa-Aguirre, 2004). *Saffron* can interfere with cancer at initiation and promotion stages as well as for cancer treatment (Das et al., 2010). Besides, diethylnitrosamine which is present in tobacco smoke, cosmetics, gasoline, and various processed foods such as milk and meat products is one of the most important environmental carcinogens (Park et al., 2009). Diethylnitrosamine induced an increase in the number and the incidence of hepatic dyschromatic nodules while *Saffron* significantly reduced the diethylnitrosamine (Amin et al., 2011). In conclusion, Saffron has been proposed as a promising candidate for treating liver cancer.

3. BIOACTIVE COMPOUNDS FROM THE MEDICINAL PLANT FOR TREATMENT OF LIVER CANCER

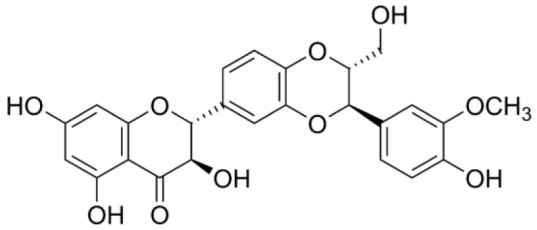
3.1 Silibinin

Silybin is a natural polyphenolic flavonoid. It is the main bioactive component of silymarin isolated from the plant milk thistle (*Silybum marianum*). It has been widely used in Asia and Europe to treat liver diseases. It is well known that milk thistle is safe and well-tolerated, and it protects the liver from drug or alcohol-related injury (Jacobs et al., 2002; Lieber et al., 2003). Studies demonstrated silibinin's inhibitory effects on multiple cancer cell lines, including prostate (Singh et al., 2003), colon (Yang et al., 2003). Moreover, silibinin treatment resulted in potent inhibition of four different human HCC cell lines (Lah et al., 2007). Silibinin at IC_{25} (120 μmol/L) and IC_{50} (240 μmol/L) doses for HuH7 cells also resulted in reduced growth of Hep3B, HepG2, and PLC/PRF/5 cells (Lah et al., 2007; Varghese et al., 2005).

3.2 Organosulfur Compounds (Oscs)

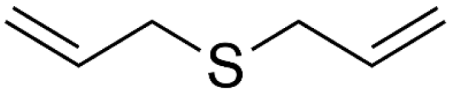
Organosulfides compounds (OSCs) occur naturally, particularly in many plant foods. The steam distillation method is widely used to extract and condense volatile OSCs from *Garlic* currently. The final

Figure 1. Structure of Silibinin



oily product is called garlic oil (GO), which contains more than 30 OSCs (Wu et al., 2001). It has been reported that the three major components involved in GO are diallyl trisulfide (DATS), diallyl disulfide (DADS) and diallyl sulfide (DAS) (Zhang et al., 2012). The *in vivo* chemoprotective effect of GO on N-nitrosodiethylamine (NDEA) induced hepatocarcinoma was demonstrated (Zhang et al., 2012). This chemoprotective effect of GO may be associated with inducing apoptosis and enhancing antioxidant activity. Moreover, OSCs have been shown to modulate the activity of glutathione S-transferases (GST), a family of enzymes important in detoxification of carcinogens. DAS treatment caused a significant increase in GST activity and was also assessed on glutathione (GSH) peroxidase activity (Gudi & Singh, 1991).

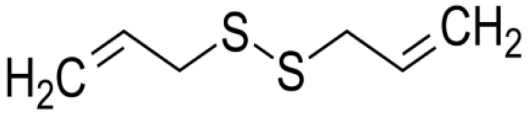
Figure 2. Structure of OSCs



3.3 Proanthocyanidin B2

Proanthocyanidins are a large class of polyphenolic compounds, which are widely found in the plants, such as grape seeds and peanut skin (Prasain & Barnes, 2014). Proanthocyanidin-B2 (PB2) consisting of two epicatechins exhibits strong antioxidant activity owing to their phenolic hydrogen atoms, which potently interrupt the free radical chain reactions (Fracassetti et al., 2013). The anti-carcinogenic properties of these compounds have been primarily attributed to their potent antioxidant and anti-inflammatory efficacy (Al-Ishaq et al., 2020; Nandakumar et al., 2008). In addition, emerging evidence suggests that these compounds may exert pleiotropic anticancer effects by targeting multiple pathways, including NF-κB, AMPK, Wnt β-catenin, cell apoptosis, PI3K/AKT, mTOR, and MAPK (Choy et al., 2016). PB2 inhibited nuclear translocation and the expression of PKM2, therefore disrupting the interaction between PKM2/HSP90/HIF-1α, to trigger apoptosis in HCC via HIF-1α-mediated transcription suppression, and suppress aerobic glycolysis and proliferation (Feng et al., 2019).

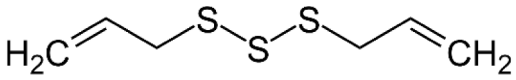
Figure 3. Structure of Proanthocyanidin B2



3.4 Quercetin

Quercetin (3, 3¢, 4¢, 5, 7-pentahydroxyflavone) is a flavonoid compound from many medicinal plants. Quercetin has received increasing attention with specific and almost exclusive activity on tumor cells rather than normal, non-transformed cells (Du et al., 2010; Park, 2011). Quercetin also exhibits a protective effect against AFB1-mediated liver damage *in vivo* by promoting antioxidative defense systems and inhibiting lipid peroxidation (Choi et al., 2010). Furthermore, quercetin reduces the hepatic cytochrome P450 content and increases the hepatic glutathione S-transferase (GST) activity involved in the activation/detoxification of chemical mutagens/carcinogens (Wiegand et al., 2009). The combined treatment of quercetin and DOX may be beneficial against human liver cancer, since quercetin can reduce the hepatotoxicity of DOX in normal liver cells (Wang et al., 2012).

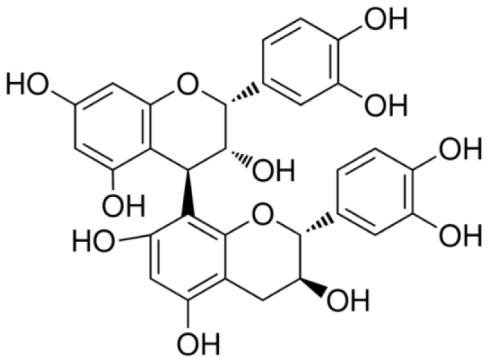
Figure 4. Structure of Quercetin



3.5 Wogonin

Wogonin (WG; 5,7-dihydroxy-8-methoxy flavone) is a naturally occurring flavonoid and was isolated from the root of *Scutellaria baicalensis*. WG is also a traditional Chinese herbal medicine that is widely used in the treatment of inflammatory conditions. Because WG has multiple pharmacological benefits including anti-inflammatory, anti-hepatitis B virus, anti-oxidant, anticonvulsant, and neuroprotective effects, as well as anti-cancer effects, it has attracted considerable attention (Chi et al., 2001; Guo et al., 2007; Li-Weber, 2009; Lim et al., 2010; Park et al., 2007; Shieh et al., 2000). WG has promising therapeutic potential as an anti-tumor agent both *in vitro* and *in vivo*, which has been clearly shown with new data continuously emerging. WG can produce anti-cancer effects by inhibiting proliferation, inhibiting angiogenesis, inhibiting cell migration, inducing differentiation, inducing apoptosis, increasing cytotoxicity, and reversing drug resistance (Dong et al., 2011; Himeji et al., 2007; Huang et al., 2012; Lee et al., 2012; Lu et al., 2008; Yang et al., 2009).

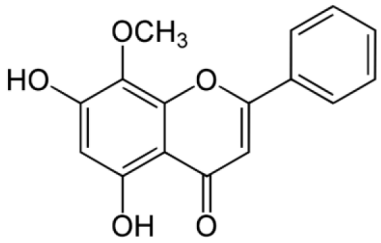
Figure 5. Structure of Wogonin



3.6 Baicalein

Baicalein (5,6,7-trihydroxyflavone), a bioactive flavonoid, is derived from the root of *Scutellaria baicalensis* or *Scutellaria radix*. The anti-tumor activity of Baicalein in HCC has been reported *in vitro* (Matsuzaki et al., 1996; Motoo & Sawabu, 1994). Inhibition of MAPK/ ERK signaling and induction of apoptosis by Baicalein treatment are critical mechanisms by which baicalein inhibits HCC growth (Liang et al., 2012). Moreover, baicalein can induce SMMC-7721 cell apoptosis through regulating PI3K/Akt signaling pathway. The combination of baicalein and LY294002 further restrained liver cancer cell proliferation and induced cell apoptosis, providing theoretical basis for liver cancer treatment (He et al., 2018).

Figure 6. Structure of Baicalein

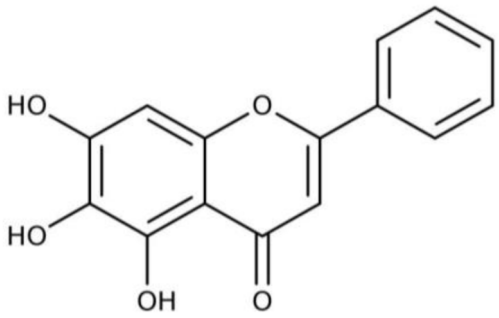


3.7 Luteolin

Luteolin (3¢,4¢,5,7-tetrahydroxyflavone) is a widely used flavonoid compound which is produced in numerous types of plants, such as vegetables, fruits and medicinal herbs. Previous studies have revealed that luteolin exhibits diverse biological properties, such as antioxidant (Ashokkumar & Sudhandiran, 2008), anti-inflammatory (Nishitani et al., 2013) and anti-proliferative effects (Ashokkumar & Sudhandiran, 2011). Notably, the sensitivity of cancer cells to chemotherapy was increased by food supplementation with LUT. JNK-mediated DR5 upregulation by luteolin sensitizes Huh7 liver cancer cells to TRAIL-

induced cell death by promoting an autophagic flux (Nazim & Park, 2019). Moreover, luteolin has the anti-hepatocarcinogenic effects in diethylnitrosamine-intoxicated mice (Zhang et al., 2016).

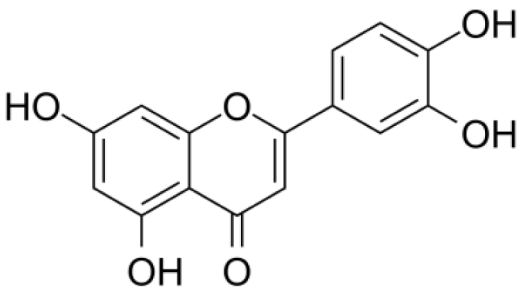
Figure 7. Structure of Luteolin



3.8 Stigmasterol

Stigmasterol, belonging to the group of phytosterol, was isolated from *Navicula incerta* organic extract. Phytosterol has apoptosis inductive effects in some kinds of carcinoma cell lines according to some previous studies such as human prostate cancer cell (LNCaP) (von Holtz et al., 1998), human colon cancer cell (HT-29) (Awad & Fink, 2000). Besides, the apoptotic inductive effect of stigmasterol was also explored in detail using hepatocarcinoma cell line HepG2 (Kim et al., 2014). This study showed that the stigmasterol-induced apoptosis was mediated through the intrinsic mitochondrial pathway which leads to the activation of caspase cascade and subsequent cell death. In conclusion, stigmasterol possesses potential apoptosis inductive effects and it could be developed as a potential candidate for hepatic cancer treatment with further studies.

Figure 8. Structure of Stigmasterol



4. PROSPECTIVE OF MEDICINAL PLANT IN THE TREATMENT OF LIVER CANCER

The potential values of herbal formulas in treating various diseases are well known. To explore the mechanisms of action by herbal formulas in liver cancer management, extensive laboratory experiments have been conducted.

In Peru, traditional complementary and alternative medicine (TCAM) coexists with conventional medicine. Plant species used in TCAM treatments for liver cancer included statistically significantly *M citrifolia* and *A vera*, as well as, to a lesser extent, *A peruviana, A sativum, A muricata, C auriculatum, C lechleri, C limon, Copaifera sp, C pepo, F vulgare, N officinale, Peperomia sp, P boldus, Phyllanthus sp, Plantago sp, S peruvianum, T vulgaris, T campylodes,* and *U tomentosa* (Rojas Rojas et al., 2018).

Shen-Ling-Bai-Zhu powder (SLBZP) is a classic herbal remedy that has been used in hepatocellular carcinoma. SLBZP has the antitumor property of the formula in hepatoma. Moreover, the therapeutic merit of SLBZP coupled with chemotherapy for hepatoma was shown because SLBZP involved descending levels of tumor growth promoters and apoptotic suppressor proteins (Xi et al., 2016).

JDF granule, comprising detoxifying endotoxic herbs, has been commonly used in Chinese traditional medicine. Some compositions of the formula have demonstrated cytotoxic activity against several hepatoma cells such as SMMC-7721 and BEL-7402 (Xu et al., 2010). Besides, the prognosis of hepatocellular carcinoma patients was considerably improved by JDF granule (Yu et al., 2009).

Yang-Gan Jie-Du Sang-Jie (YGJDSJ) was established for hepatoma treatment based on clinical medications and related studies. They evaluated the anticancer potential of YGJDSJ on suspension human hepatocellular carcinoma Bel-7402 cells because YGJDSJ inhibited anchorage-independent growth and induced caspase-mediated anoikis in Bel-7402 cells, which may be related to ROS generation and PTK2 downregulation (Hu et al., 2018).

5. CONCLUSION

Many medicinal plants have been shown may be applied to reduce signals and towards the treatment of liver cancer. Currently, the use of herbs in the treatment of liver cancer is getting more attention due to fewer side effects than the treatment with chemically synthesized drugs. Moreover, many bioactive compounds are presented in medicinal plants. It would be important to find new bioactive compounds and study deeper details about medicinal plants against liver cancer.

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Chapter 12
Effects of Nigella sativa and Its Active Ingredient Thymoquinone on Breast Cancer

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ABSTRACT

Breast cancer (BC) is the most prevalent malignancy in women. The main treatment for BC is surgery and chemotherapy. Generally, the chemotherapeutic drugs used for treatment cause numerous side effects. Substances derived from natural products have proven to exhibit anti-cancer effects without causing side effects. For instance, biochannin A found in cabbage and cauliflower reduced the growth of estrogen dependent MCF 7 cells. Another example is curcumin present in turmeric exhibits anti-proliferative and inhibitory effect against BC. The active compound of Nigella sativa is thymoquinone. The oil extracted from Nigella sativa reduced blood pressure. Nigella sativa exerts anti-pyritic, anti-inflammatory, and anti-microbial activity. Thymoquinone is found in seeds of Nigella sativa. Thymoquinone is a promising anti-neoplastic, anti-carcinogenic, anti-proliferative agent. In this chapter, the authors emphasize the anticancer potential of Nigella sativa and its derivatives and the mechanism of action against BC.

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INTRODUCTION

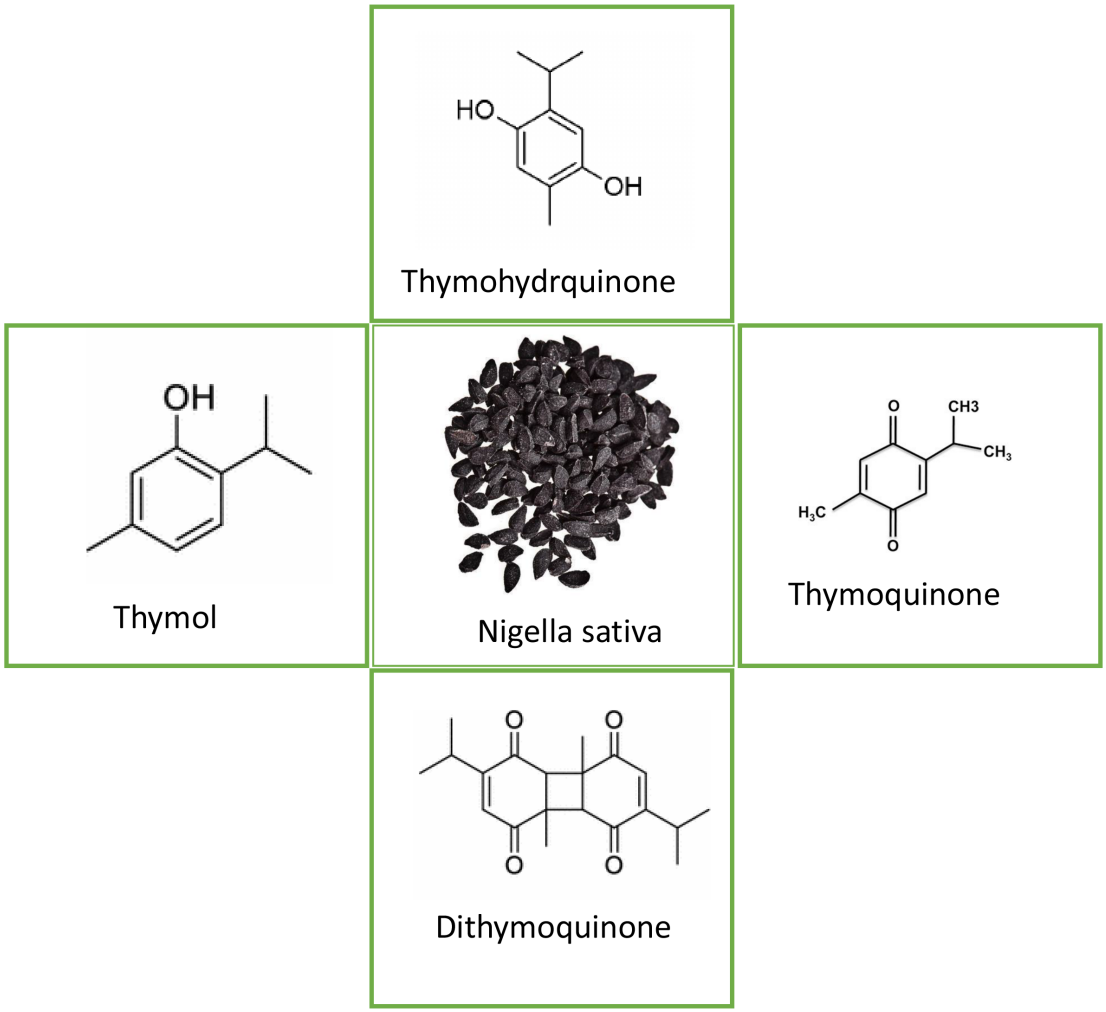
Breast cancer (BC) is the most prevalent malignancy in women (Wörmann et al., 2017). In males it occurs with low frequency (Abdelwahab Yousef, 2017). Worldwide, BC is a major cause of women's suffering and premature mortality. BC causes more cancer deaths in women in the United States than in any other place (Coughlin, 2019). According to estimates from WHO 2012, one in three women in Asia faces the possibility of BC in their lifetime (Donepudi et al., 2014). Indian women are affected at a possible rate as high as 25.8 per 100,000 women and 12.7 per 100,000 women mortalities (Malvia et al., 2017). Different profiles of hormone receptors may be expressed by breast cancers: ER (+)/PgR (+), ER (-)/PgR(-), ER(+)/PgR(-) and ER(-)/PgR(+) (Kunc et al., 2018). The expression of progesterone receptors (PR) along with the ER is evaluated as a prognostic factor (Lamb et al., 2019). Triple-negative breast cancer (TNBC) is a heterogeneous group of tumors composed of distinct BCs that are simply distinguished by the absence of estrogen receptor, progesterone receptor, and overexpression of gene receptor 2 human epidermal growth factor (Kumar et al., 2016).

The primary treatment for BC is surgery accompanied by chemotherapy and radiation therapy. Chemotherapeutic drugs used in the treatment of BC such as doxorubicin, docetaxel causes severe side effects which includes infertility, heart damage, leukemia. It is important to reduce the side effects as well as to decrease the cancer development (Shinden et al., 2020). Several studies shows that products derived from natural substance exhibits anticancer effects and decrease the aggressiveness of BC and inhibit cancer cell proliferation and regulate cancer related pathways. Natural product has the ability to provoke many physiological pathways which can suppress the effect of stubborn disease like cancer (Cragg et al., 2005). The phytochemicals present in the natural compounds aids in suppressing the adverse effect of conventional treatment (Somasundaram et al., 2002; Pandurangan and Mustafa, 2018; Suresh Kumar et al., 2019; Sivaprakasam et al., 2020).

Some of the natural products has already been reported to exhibit anticancer activity. 3,3'-Diindolylmethane (DIM) is a product of indole-3-carbinol acid condensation and is a natural compound found abundantly in broccoli, cauliflower and cabbage (Verhoeven et al.,1996). DIM has been reported to induce apoptosis by arresting G2/M cell cycle phase and sense gamma radiation and increase ROS production (Li et al., 2010). It was also enhanced the cyp19 expression and acts as aromatase inhibitor in MDAMB-231 and MCF-7 cells (Licznerska et al., 2016). Biochanin A obtained from red clover is an isoflavone that exhibits anticancer activity. It has been reported that Biochanin A reduced the growth of estrogen dependent MCF-7 cells at lower concentration (Yu et al., 2019). Curcumin a polyphenolic compound found in turmeric exerts anti-breast cancer activity by inducing apoptosis and apoptosis related genes. It exhibited its anti-proliferative effect by suppressing the expression of NF-κB in MDA MB-231 cells (Ghasemi et al., 2019). It's also reported that curcumin inhibits BC by blocking Wnt signaling pathway in MCF-7 cells. It also increases the effect of chemotherapeutic agent (Marquardt et al., 2015). Epigallocatechin is a phenolic catechin found in green tea. It induces apoptosis in ER negative MDA MB-468 and MDA MB-231 cells (Meeran et al., 2011).

Nigella sativa is commonly known as black cumin, nigella, kalajeera (Amin et al., 2016) It is found mostly in Eastern Europe and Western Asia (Shabana et al.,2013). *Nigella sativa* is used to treat diseases including Asthma, Diarrohea and dyslipidaemia (Ali et al., 2003). The active principles include thymoquinone, thymohydroquinone, dithymoquinone (nigellone), thymol, carvacrol, nigellicine, nigellidine and hedrin (Figure 1) (Singh et al., 2014). The oil extracted from Nigella sativa reduces blood pressure (Mohtashami et al., 2019) and increases respiration (El Tahir et al., 1993). Nigella sativa also exerts

Figure 1. The active principles compounds of Nigella sativa were represented



various pharmacological activity which includes antipyritic, (Al-Ghamdi, 2001), anti-inflammatory (Gholamnezhad et al., 2016), analgesic (Amin et al., 2016), antimicrobial (Ikhsan et al., 2018) and anticancer (Randhawa et al., 2011). Silver nano particles isolated from seeds of nigella sativa contains phenols, terpenoids, and flavonoids has reported that it inhibits the development of tumor by promoting apoptosis and regulating the expression of Bax, Bcl-2 and COX-2 in MCF-7 cells (Rohini et al., 2019). Aumeeruddy et al., (2019) reported the anticancer effect of nigella sativa along with piperine and sulforaphane. Nano emulsion prepared using *Nigella sativa* essential oil also plays an important role in breast cancer by inducing apoptosis that includes cell membrane blebbing, cytoplasmic vacuolation and fragmentation of nucleous in MCF-7 cells (Periasamy et al., 2016).

Thymoquinone (2-isopropyl-5-methylbenzo-1, 4-quinone) is a major bioactive compound found in the seeds of nigella sativa. It is also found in various medicinal plants belonging to various families such as Juniperus (Imran et al., 2018). Thymoquinone exhibits various pharmacological including anti-

oxidant and anti-inflammatory activity. Thymoquinone is a hydrophobic molecule which can affect it's bioavailability and drug formulation. The stability of thymoquinone decreased with increasing PH and degraded at higher rate at acidic PH (Ali et al., 2020). Thymoquinone exhibits antioxidant activity by scavenging ROS including superoxide anion, Hydroxyl radical and singlet molecular oxygen (Woo et al., 2011). Thymoquinone enhanced the plasma and liver antioxidant capacity and increase the expression of liver antioxidant genes. Thymoquinone protected several organs from oxidative damage induced by free radicle generating agent (Abdel-Daim et al., 2020). Thymoquinone exhibits promising anti-carcinogenic, anti-neoplastic, anti-proliferative and anti-proliferative agents against different tumor models, anti-mutagenic activities (Gholamnezhad et al., 2016).

MOLECULAR TARGETING OF AKT BY THYMOQUINONE PROMOTES G1 ARREST BC CELLS

Thymoquinone induced cytotoxicity at the concentration of 60 to 90 μM after treatment of 12 hours in ER positive cells such as MCF-7 and T-47D and ER negative cells such as MDA-MB-231 and MDA-MB-468 cells were observed through MTT assay. Thymoquinone induces G0/G1 phase cell cycle arrest after 12- and 24-hours incubation. Thymoquinone promoted apoptosis at 48 hours treatment by shifting G1 phase cell cycle arrest to sub G1 phase. Through trypan blue dye exclusion test indicated that thymoquinone decreased cell viability in time dependent manner and induction of apoptosis by thymoquinone was observed through TUNEL staining. Hoechst staining indicated that thymoquinone cause nuclear morphological changes including chromatin condensation. Thymoquinone treatment after 24 and 48 hours increased the expression of p27 which is a Cdk inhibitor. Thymoquinone suppressed the expression of cyclin D1 and cyclin E and downregulated antiapoptotic proteins such as Bcl2 and survivin and also upregulated the expression of pro apoptotic protein such as Bax and p53.Thymoquinone induced apoptosis by blocking PI3K/Akt signaling pathway by regulating the expression of PDK1, PTEN, Akt, GSK-3β, pro-caspase-9 and Bad. TQ has interfered with mTOR mediated by Akt. Based downstream objectives through the deregulation of phosphorylation of 4E-BP1 that is associated with eIF4E firm binding that avoids Complexity in the development of functional cap binding, resulting in Cyclin D1 translational repression. Thymoquinone inhibited Akt regulated mTOR dependent translational inhibition of cyclin D1 in breast cancer cells (Rajput et al., 2013).

THYMOQUINONE INHIBITS TUMOR GROWTH AND INDUCES APOPTOSIS IN BC XENOGRAFT MODEL

It was reported that Thymoquinone treatment induces apoptosis via inducing ROS in BC cells and xenograft model (Woo et al., 2013). The result of western blot analysis indicated that thymoquinone upregulated the phosphorylation of MAPK in MCF-7 cells. Increased JNK and p38 protein phosphorylation was observed after 12 hours of treatment. P38 MAPK ELISA kit indicated that thymoquinone increased the p-p38 level in MCF-7 cells and MDA-MB-231 cells after 12 hours of treatment at a concentration of 40μM and this increase can also be reversed by treatment with SB203580. Thymoquinone induced anti-proliferative effect and suppressed anti-apoptotic genes. thymoquinone induced ROS production promoting apoptosis in MCF-7 cells and this production can be reversed by pretreatment with NAC.

Thymoquinone induced ROS regulates the phosphorylation of p38 in MCF-7 cells. Thymoquinone and doxorubicin at concentration of 4mg/kg and 2.5 mg/kg respectively reduced the tumor growth in nude mice model. Thymoquinone treatment increased the catalase level, SOD and glutathione level in liver tissue of mouse xenograft model. Therefore, thymoquinone can suppress human breast cancer cells both *in-vitro* and *in vivo* models (Woo et al., 2013).

THYMOQUINONE POTENTIATES TAMOXIFEN IN HUMAN BREAST CANCER CELLS

Thymoquinone and tamoxifen together reduced the cell viability of MDA-MB-231 and MCF 7 cells which was observed through MTT assay after 24 hours and 48 hours of treatment at concentration of 150 μM, without causing cytotoxicity. Early apoptotic cell morphologies were observed through AO-EB staining in both MDA-MB-231 and MCF-7 cells. The data obtained from AO-EB staining was confirmed by TUNEL staining. It showed thymoquinone and tamoxifen together increased the apoptotic index in both MDA-MB-231 and MCF 7 cells after 48 hours of treatment. This shows that thymoquinone can be used to reduce the treatment of breast cancer with high concentration of tamoxifen (Ganji-Harsini et al., 2016).

THYMOQUINONE POTENTIATED CYCLOPHOSPHAMIDE-MEDIATED INHIBITION OF CELL PROLIFERATION

The result of cell cytotoxicity assay indicated that thymoquinone along with cyclophosphamide inhibited cell proliferation and cell viability in SKBR-3 and MDA-MB-231 cells at a concentration of 10mM and 20mM along with constant dose of 0.5mM cyclophosphamide. Thymoquinone along with cyclophosphamide induced cell cycle arrest in G1 and sub G1 cell cycle phase in both Her^{2+} and Her^{2-} BC cells. Thymoquinone and cyclophosphamide regulates Akt/PI3K/mTOR pathway by downregulating the phosphorylation of Akt. It also decreased the expression level of cyclin D1 which is a Her2 regulator. Thymoquinone also can induce cell death independent of FASN mediated signaling. This study indicates that thymoquinone can inhibit cell proliferation independent of changes in the expression of Her2 and increases the efficiency of cyclophosphamide at lowest concentration of 0.5mM (Khan et al., 2019).

CO_2 Extract of Nigella Sativa Against Breast Cancer Cells

CO_2 were used to extract from Nigella sativa at various pressure and temperature. The A3 is a CO_2 extract of Nigella sativa prepared at 2500 psi and 60^0c exhibited cytotoxicity and inhibited cell viability in MCF7 cells at a concentration of 100 μg/mL. A3 extract activated proapoptotic proteins in dose and time dependent manner. It increased the level of caspase 3 and 7 at 100 and 80 μg/mL respectively and increased the level of caspase 8 at concentration of 100 and 120 μg/mL after 9 hours of treatment. Hoechst 33258 stain showed the effect of A3 on nuclear morphology in MCF7 cells. A3 extract treatment exhibited nuclear shrinkage, chromatin condensation and nuclear fragmentation in MCF-7 cells after 24 hours of treatment. The cell treated with 40 and 80 μg/mL showed apoptosis, cell membrane disruption, blebbing and various sized vacuoles and chromatin condensation after 24 hours of treatment. A3 treatment also Inhibited the clonogenicity of MCF 7 cells at higher concentration. It also inhibited

cancer cell migration at concentration of 20 and 40 µg/mL after 12 hours of treatment. The cytotoxicity percentage increased after 24 hours of A3 treatment. Cell invasion assay performed on Matrigel matrix showed that A3 treatment Inhibited cell invasion at a concentration of 20 and 40 µg/mL after 24 hours of treatment. These results indicate the anti-metastatic ability of A3 extract of Nigella sativa against BC cells (Baharetha et al., 2013).

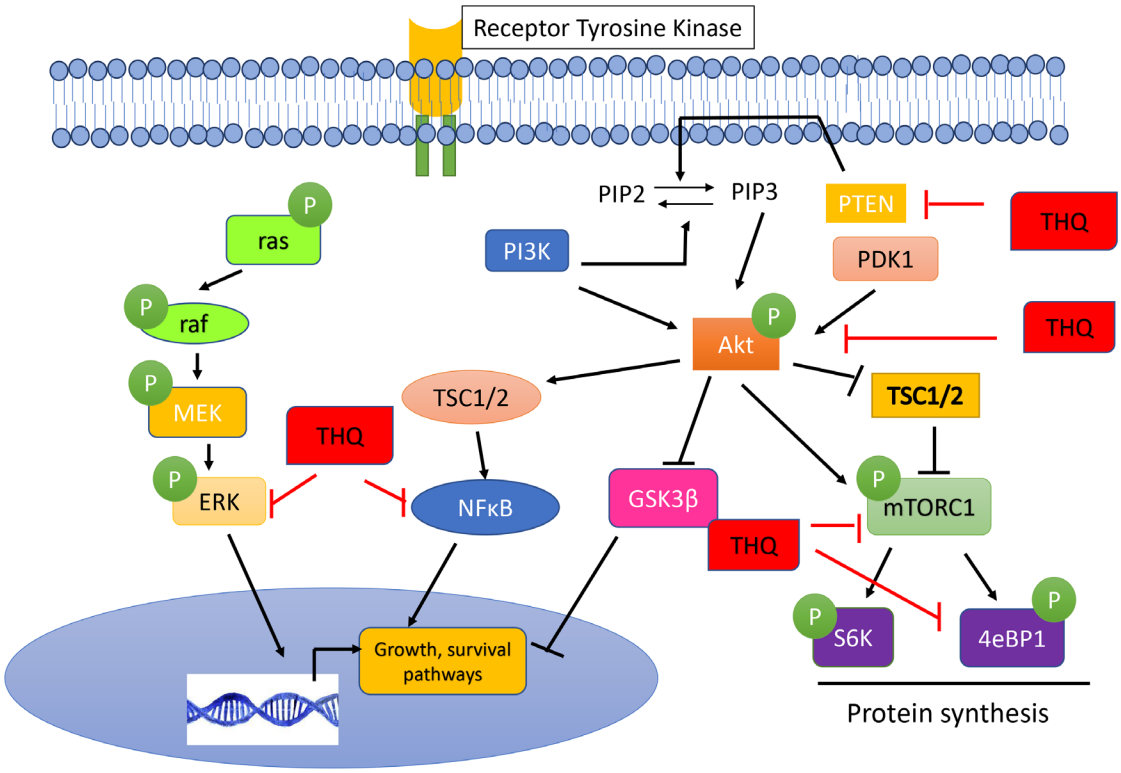
THYMOQUINONE UP-REGULATES PTEN EXPRESSION AND INDUCES APOPTOSIS IN BC CELLS

Thymoquinone inhibited cell proliferation of MCF7/DOX cells in time and dose dependent manner. MCF 7/DOX is a doxorubicin resistant human breast adenocarcinoma MCF 7 cell lines. MTT assay indicated that thymoquinone at a concentration of 100µM inhibited cell proliferation to 65 percentage after 48 hours of treatment. Thymoquinone induced apoptosis in MCF7/DOX cells along with morphological changes such as fragmented nuclei and apoptotic bodies were observed by fluorescence microscopy when stained with Hoechst dye. The mitocapture reagent did not aggregate in the mitochondria indicating that thymoquinone has disrupted mitochondrial membrane potential and activating caspase pathway. Thymoquinone induced p53 dependant and independent apoptosis by decreasing Bcl2 and increasing Bax Protein level. Thymoquinone induced G2/M cell cycle phase arrest in MCF 7/DOX cells. Thymoquinone also reduce the level of Cdc25c and cyclin B1 and it also induced DNA damage. The result of western blot analysis indicated that thymoquinone increased the level of PTEN while decreasing the level of p-Akt level in MCF 7/DOX cells indicating that regulation of PTEN/Akt pathway is associated with thymoquinone induced growth inhibition, apoptosis and cell cycle arrest. Therefore, thymoquinone induced apoptosis by upregulating PTEN at transcriptional level in doxorubicin resistant MCF 7 cells (Arafa et al., 2011).

Thymoquinone Inhibits Bone Metastasis of Breast Cancer Cells

Shanmugam et al., (2018) reported that, Thymoquinone suppressed the expression level of CXCR4 in MCF 7 and MDA-MB-231 cells at a concentration of 50 µM in time and dose dependent manner. When cells pretreated with ALLN, a proteasome inhibitor and chloroquine, a lysosomal inhibitor also induced downregulation of CXCR4 when treated with Thymoquinone indicating that thymoquinone induced downregulation of CXCR4 is not mediated by degradation. Thymoquinone suppresses the activation of NF-κB expression in time dependent manner indicating that Thymoquinone may downregulate CXCR4 expression via preventing activation of NF-κB. It also suppressed the nuclear accumulation of p65 and phospho-p65 in MDA-MB-231 cells. Thymoquinone also suppressed CXCL12 induced overexpression of CXCR4 in MDA-MB-231 cells. Thymoquinone inhibited the expression of CXCR4 by preventing NF-κB binding to the CXCR4 promoter. Thymoquinone inhibits CXCL12 cellular invasion and migration in both MDA-MB-231 and BT-549 cells. Thymoquinone also inhibited tumor growth and reduced vascular volume in CAM assay model. Thymoquinone treated metastatic murine model suppressed the metastatic activity after 4 weeks. It also decreased the metastatic sites and also bone colonization of breast cancer cells. Thymoquinone exerted its anti-metastatic effect in lungs and brain tissue. Thymoquinone treatment prevented thinning of bone in murine model. Thymoquinone also reduced the expression of NF-kB regulated genes that are involved in tumor growth, metastasis and angiogenesis in the tumor tissues. Thymoquinone treatment also decreased the expression of CXCR4 in femur of mice and similar

Figure 2. The regulation PI3K/Akt signaling were mTOR signaling act as downstream to Akt signaling. Thymoquinone (THQ), inhibits the phosphorylation of Akt. On the other hand, it activates the PTEN expression that inhibits Akt. THQ directly suppress the expressions of mTORC1 and 4eBP1



effect was observed in lungs and brain tissue when treated with thymoquinone. Thus, Thymoquinone can effectively inhibit NF-kB regulated CXCR4 expression, invasion, migration in TNBC cells along with suppressing bone metastasis (Shanmugam et al., 2018).

Regressions of Breast Carcinoma Syngraft with Piperine and Thymoquinone

Thymoquinone at a concentration of 10-800μM and Piperine at a concentration of 50-1200 μM synergistically inhibits EMT/P cell proliferation in dose dependent manner in mouse breast cancer cells. Thymoquinone and Piperine combined together effectively Inhibited the expression level of vascular endothelial growth factors. Thymoquinone and Piperine exerted its anti-tumor effect by reducing the tumor size in tumor bearing mice model. TUNEL colorimetric assay result indicated high level of apoptosis in tumor section when treated with thymoquinone and Piperine. It also increased the activity level of caspase-3 in time dependent manner. Synergistic therapy also induced extensive necrosis. Increased level of IFN-γ, IL-2, IL-4 and IL-10 was observed in thymoquinone and piperine treated mice models. Thymoquinone and Piperine decreased the level of AST, ALT, and creatinine indicating that the treatment caused no liver or kidney toxicity. Thus, thymoquinone and Piperine can synergistically inhibit breast cancer *in vivo* and *in-vitro* (Talib et al., 2017)

ANTICANCER ACTIVITY OF THYMOQUINONE IN BREAST CANCER CELLS

Shanmugam et al., (2018) reported that, administration of Thymoquinone to breast cancer cells exerted anti-proliferative effect in MCF-7, MDA-MB-231 and BT-474 cells at a concentration 32 μM, 11 μM, and 21 μM respectively after 48 hours of treatment. Thymoquinone also enhanced the cytotoxic effect of doxorubicin, 5-fluorouracil. Thymoquinone induced cell death through apoptosis in MCF-7 cells through activation of caspase 8,7 and 9. It also increased the level of Bcl-2, an anti-apoptotic protein and increased the expression level of pro apoptotic protein such as Bax. Thymoquinone reduced the migration of MCF7 and MDA-MB-231 in dose dependent manner. Thymoquinone also inhibited invasion in MDA-MB-231 in dose dependent manner. Thymoquinone also enhanced the level of PPAR alpha, PPAR gamma/delta in MCF 7 cells. It decreased the level of Bcl-xL, survivin in time dependent manner at mRNA and protein level. The results indicated that Thymoquinone could reduce survivin expression through the activation of PPAR-gamma pathway (Woo et al., 2011).

NIGELLA SATIVA EXTRACT REDUCED THE TUMOR FORMATION IN DMBA-INDUCED BREAST CANCER

Thymoquinone and black cumin seed oil decreased the level of MDA, LDH, ALP, and AST induced by DMBA at a high concentration in female rat model. Both thymoquinone and black cumin seed oil stimulates the mammary gland and inhibits the progression of Mammary tumor cell proliferation. Black cumin seed oil exerts it's anti-neoplastic and anti-carcinogenic activity in DMBA induced breast cancer female rat. DMBA induced breast cancer is accompanied by increased oxidation process while Nigella sativa decreases the oxidation level by exerting it's anti-oxidant effect. Thymoquinone and black cumin seed oil decreased the expression level of BRCA1, BRCA2, Id- and P53 mutations in mammary tissues of DMBA induced breast cancer female rats. Both Thymoquinone and Black cumin seed oil does not cause any toxicity to the female rats. Thus, Thymoquinone and black cumin seed oil exert protective effect against DMBA induced breast cancer in female rat model (Linjawi et al., 2015).

THYMOQUINONE INDUCES APOPTOSIS VIA NADHP QUINONE OXIDOREDUCTASE IN BREAST CANCER CELLS

Thymoquinone reduces the number of MDA-MB-231, MDA-MB-468, and T-47D breast cancer cells at a concentration of 2.5–25μM after 24h of treatment. MDA-MB-468 was highly sensitive to thymoquinone while MCF 7 cells were resistant to the concentration of Thymoquinone that is cytotoxic to other breast cancer cell lines. However, thymoquinone reduced the number of MCF7 cells after 24hours of treatment at a concentration of 100μM. Thymoquinone induced extensive apoptosis in MDA-MB-468 cells while low apoptotic death in MCF-7 cells. Thymoquinone induced p53 independent apoptosis in MDA-MB-468 cells. Thymoquinone also reduced the protein level of survivin. NQO1 is a multifunctional cytoprotective flavoprotein is found to be abundant in thymoquinone resistant MCF-7 cells while the expression level of NQO1. Was found to be decreased in thymoquinone sensitive MDA-MB-468 cells from the results of western blot analysis. Inhibition of NQO1 by dicoumarol at a concentration of 5 μM makes MCF-7 cells sensitive to thymoquinone which aids in exerting its anticancer effect. It was

concluded that thymoquinone can be used as natural agent to treat breast cancer with high expression level of NQO1 (Sutton et al., 2012).

MEHTANOLIC EXTRACT OF NIGELLA SATIVA MODULES THE P53 IN MCF-7 CELLS

Methanolic extract of *Nigella sativa* seed exerted its cytotoxicity effect inhibition cell proliferation in dose dependent manner at the highest concentration which is 125 µL/mL in MCF-7 cells. Almost 87 percentage of MCF-7 cells treated with *Nigella sativa* were observed dead after 48h of treatment. The result of TUNEL assay indicated that *Nigella sativa* induced apoptosis in MCF7 cells in dose and time dependent manner. About 76 percentage of Nigella sativa treated MCF7 cells went apoptosis after 72 hours of treatment. *Nigella sativa* increased the expression level of caspase-3, caspase-8, caspase-9 and p53 by several folds in concentration dependent manner. Thus, *Nigella sativa* induced apoptosis in MCF7 breast cancer cells is due to nuclear and mitochondrial pathway. Thus, *Nigella sativa* exerts its anticancer activity by inhibiting proliferation and inducing apoptosis by regulating pro apoptotic genes in MCF7 cells (Alhazmi et al., 2014).

RADIOSENSITIZATION IN HUMAN BREAST CARCINMOA CELLS BY THYMOQUINONE

Thymoquinone in combination with IR radiation at 2.5 Gy reduced cell proliferation of MCF7 and T47D cells in concentration dependent manner after 24 hours of treatment. MTT assay indicated that T47D cells were more sensitive to thymoquinone than MCF7 cells. Anti-proliferative effect of Thymoquinone increased when the cells were treated with IR radiation along with Thymoquinone. IR radiation and thymoquinone combined reduced the colony forming ability of MCF7 and T47D breast cancer cells. Thymoquinone at a concentration of 50 µM and IR radiation at 2.5Gy induced approximately 55 and 68 percentage of apoptosis in MCF7 and T47D breast cancer cells respectively. IR-induced DNA damage activates checkpoint or irreversible growth arrest that results in cell death. Thymoquinone and IR radiation treatment induced G2-M phase cell cycle arrest in both MCF7 and T47D breast cancer cells. Thus, Thymoquinone combined with IR radiation induces high toxicity in T47D cells than MCF7 cells by regulating apoptosis (Velho-Pereira et al., 2011).

ANTIPROLIFERATIVE PROPERTIES OF METHANOLIC EXTRACT OF NIGELLA SATIVA

Dilshad et al., (2012) reported that, methanolic extract of *Nigella sativa* induces apoptosis in MDA-MB-231 cells. The results of SYBR green based real time PCR indicated that the Methanolic extract of *Nigella sativa* Increased the expression of Bax and caspase-3 and decreased the expression of Bcl2 which is an anti-apoptotic protein at a concentration of 2.5 µg/mL or 5 µg/mL after 48h of treatment in MDA-MB-231 cancer cells. *Nigella sativa* also induced DNase mediated DNA cleavage leading to apoptosis in dose dependent manner. *Nigella sativa* treated cancer cells showed cell cycle arrest in sub

G0/G1 phase. Nigella sativa reduced both cancer cell growth and cell number. *Nigella sativa* increased the expression level of p53 inducing DNA damage in MDA-MB-231 cancer cells. Thus, Methanolic extract of *Nigella sativa* exhibits anticancer activity by regulating apoptotic genes in MDA-MB-231 cancer cells (Dilshad et al., 2012).

THYMOQUINONE INHIBITS CELL PROLIFERATION, MIGRATION, AND INVASION IN TNBC CELLS

Thymoquinone inhibits cell viability in MDA-MB-231, MDA-MB-436, and BT-20 after 72h of treatment at a concentration range of 7.5-10 μM and 15-20 μM respectively. Thymoquinone also reduced the ability of colony formation in both MDA-MB-231and MDA-MB-436. Thymoquinone decreased migration and invasion ability of MDA-MB-231and MDA-MB-436 by 70 and 75 percentage respectively at a concentration of 10 μM. Thymoquinone decreased invasion ability of MDA-MB-231and MDA-MB-436 by 92 and 93 percentage respectively at a concentration of 10 μM. Thymoquinone reduced the expression level of eEF-2K, Src and p-Akt in TNBC cells. Inhibition of eEF-2K mediates thymoquinone induced inhibition of TNBC cell migration and invasion. Thymoquinone regulates eEF-2K by modulating NF-κB/miR-603 signaling axis. Therefore, thymoquinone can be potential anti TNBC agent (Kabil et al., 2018).

CONCLUSION

Nigella sativa is regarded as the most powerful therapeutic herb. It is widely used in traditional medical systems such as Unani and Tibb, Ayurveda, and Siddha. Seeds and oil have a long history of folkloric use in many medicinal and culinary systems. N. sativus seeds has long been used to cure a variety of diseases and afflictions. N. sativa have been studied by a number of scientists, and a wide range of pharmacological actions have been discovered, including antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepato-protective, renal protective, gastro-protective, antioxidant properties, and so on. The mechanism of action of Nigella sativa and its derivative Thymoquinone against breast cancer was discussed in this chapter. In a nutshell, we assure that Nigella sativa and Thymoquinone were potent against all forms of breast cancer in the preclinical setting.

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Section 2

Active Ingredients of Natural Products as Cancer Therapeutics

Chapter 13
Flavonoids:
Their Anticarcinogenic Effects and Molecular Modeling Studies

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ABSTRACT

Flavonoids, defined as plant-derived secondary metabolites, have been widely found in nature with more than 10,000 different species, since their discovery. They are divided into subclasses based on the oxidative state of the ring, such as flavones, flavonols, flavanones, isoflavones, flavandiols, dihydroflavonols, and anthocyanidins. They are promising compounds with a wide variety of biological activities including antioxidant, antitumor, antigen-toxicity properties. Furthermore, flavonoids are seen as promising tools in the development of new drug assets, and they have been the subject of studies for the development of high-efficiency formulations for the treatment of a variety of future-threatening diseases. Molecular modeling studies play an important role in identifying the most stable molecular configurations and conformations of these molecules. This chapter focuses on the structural and functional properties of flavonoids, their biological activities, bioavailability, use in cancer, use in the development of new drugs, and molecular modeling studies on these molecules.

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FLAVONOIDS

Flavonoids, which are polyphenolic compounds, are widely found in plants in nature and the main source of yellow, blue and red pigments in plants (Harborne & Mabry, 1982), also affect the flavor of foods by given the astringent or bitter tastes in the mouth (Hufnagel & Hofmann, 2008). Plant-derived flavonides are produced secondary metabolites to attract insect pollinators by providing the formation of flower pigments, to form signal molecules for beneficial microorganisms, and as antimicrobial defense compounds for plants (Wasmann & VanEtten, 1996; Enkerli, Bhatt, & Covert, 1998).

The Interest in flavonoids, of which approximately 10000 varieties are known today, has started to accelerate since the 1940s (Middleton Jr, 1993), and today the research on evaluation of the new functions of flavonoid compounds continues. As a result of extensive research, it has been determined that flavonoids have versatile biochemical and pharmacological activities. (Holiman, Hertog, & Katan, 1996).

Flavonoids and isoflavonoids were discovered as probably the best characterized natural product pathway in plants, and there has been an explosion of interest in them as components of the human diet for their beneficial health-promoting effects. (Dixon & Steele, 1999). Flavonoids, which are found in many parts of the plant, are generally found in fruits, vegetables, seeds, flowers, leaves and branches (Cook & Samman, 1996; Havsteen, 2002). Flavonoids have two phenyl rings (A and B) linked by a heteracyclic ring composed of three carbon chain that contain oxygen (C ring). Thus, their structure is also referred to as C6-C3-C6. Depending on the carbon of the C ring on which B ring is attached, and the degree of unsaturation and oxidation of the C ring, they classified in six subgroups, namely; flavones, flavonols, flavanones, isoflavones, flavanols, flavandiols, dihydroflavonols and anthocyanidins (Kumar & Pandey, 2013; Wang et al., 2018; Jucá et al., 2020). The structural and functional diversity of flavonoids, the largest class of polyphenols, is enormous. (Rice-Evans, Miller, & Paganga, 1997; Guliyev, 1999). Flavonoids are considered essential for human health both as active components of medicinal plants and as bioactive food components (Winkel-Shirley, 2002; Shuvendu Das & Rosazza, 2006) and are an integral part of our diet as they are naturally found in fruits, vegetables, seeds and herbal products. They have been proven to be safe for the human organism and their daily intake is estimated to be around 1g per day. (Cook & Samman, 1996; Hollman & Katan, 1999; Havsteen, 2002). Flavonoids, due to their many bioactive properties including antioxidant, antiflamatuar, hepatoprotective, antimicrobial, antiviral anticancer properties (Kumar & Pandey, 2013), they have been proven by scientific studies having beneficial effects in many pathological conditions such as obesity, Parkinson's disease, Alzheimer's disease, viral infections, coronavirus infections and cancer (So, Guthrie, Chambers, Moussa, & Carroll, 1996; Youdim & Joseph, 2001; Havsteen, 2002; Pavanato et al., 2003; Crowe et al., 2011; Wedick et al., 2012). Flavonoids are also known as health-promoting "nutraceuticals" (Madhujith & Shahidi, 2006), which makes them interesting. As plant-derived natural chemicals they are biosynthesized from the phenylalanine amino acid (Winkel-Shirley, 2002; Shuvendu Das & Rosazza, 2006).

Flavonoids: Classification and Structural Characteristics

In plants, flavonoids are involved in protection from stress (e.g. against UV radiation, oxidative and heat stress), early plant development, signaling (e.g. legume nodulation), and protection from insect and mammalian herbivores (Gould & Lister, 2006). They are one of the largest classes of phenolic compounds, in the 2-phenyl-benzo-a-pyrone structure, and are found in the composition of many foods (Hertog et al., 1993; Briviba & Sies, 1994; Cook & Samman, 1996; Holiman et al., 1996; Wildman, 2001; Graf,

Milbury, & Blumberg, 2005; Wang et al., 2018). Flavonoids as 2-benzo-γ-pyrone derivatives, have a common basic structure, usually as glycosylated or esterified forms consisting of two aromatic rings (A, B) connected by oxygen-containing three-carbon ring (C) (Isoda et al., 2014; G. Wang et al., 2018; Siddiqui, Rahman, Rupasinghe, & Vazhappilly, 2020).

Flavonoids exist in the form of free aglycones, glycosides, or methylated derivatives, and the majority of naturally occurring flavonoids have been determined to be in the form of glycosides (Wildman, 2001; Graf et al., 2005; Corradini et al., 2011). They can be found as glycosides in living plant tissues like leaves, flowers, and fruits, as aglycones in woody tissues, and in both forms in seeds, depending on the plant type (Shahidi & Naczk, 1995). Flavonoids differ depending on the bonding differences between the B and C rings, the unsaturation and/or oxidation of the C ring containing different radical groups, and the presence of H and OH groups attached to the rings. (Chen et al., 2018; Wang et al., 2018). The carbon atoms in the A and C rings (in the benzopyran moiety) are numbered starting from the oxygen atom as 1, 2, .., and the B ring, starting from the carbon atom connected to the C ring with 1', 2' … numbers (Guliyev,1999). In the C ring, flavonoids are most commonly mono-, bi- or tri-hydroxylated (or methoxylated) at the 3', 4' and/or 5 positions, with hydroxylation at the 2' position being rare (Bailly, 2021). Natural flavonoids are known to include up to seven hydroxyl groups in their structure. According to the degree of glycosylation of benzene and aglycones in their basic structure, the attachment positions of sugar residues to aglycones, the structure of the oxide ring of sugars and the configuration of glycosidic bonds, flavones (e.g. apigenin, chrysin), flavanones (e.g. hesperitin, naringenin), isoflavones (e.g. daidzein, puerarin), flavonols (eg, myricetin, quercetin (QU) and rutin), catechins, flavan-3,4-diols, anthocyanins (eg, delphinidin, cyanide) and other varieties occur. Chalcones, biflavones, coumarins, aurons, and daflavonoids are also added to these classes (Pietta, 2000; Wang et al., 2018).

Dimer forms of flavonoids are also common in plants and are called biflavonoids which are formed by the condensation of flavonoid monomers. Phenolic compounds exist in different forms depending on their structural properties as well as their relationship with the food matrix. For example, they can be found in plants in covalently bonded soluble esters to low molecular mass components, such as sugars and fatty acids or conjugated free form and insoluble bonded forms (Bei, Liu, Wang, Chen, & Wu, 2017; Arruda, Pereira, de Morais, Eberlin, & Pastore, 2018; Gulsunoglu, Karbancioglu-Guler, Raes, & Kilic-Akyilmaz, 2019).

FLAVONOID TYPES

Flavones

Flavones are generally found in land-plant strains and are distributed in all parts of plants such as flowers, stems, bark and leaves (Martens & Mithöfer,2005). They composed of six membered heterocycles have a unique structure in that they contain a saturated double bond between the C2 and C3 positions and a ketone group at C4 (Panche, Diwan, & Chandra, 2016; Joshi, Kulkarni, & Wairkar, 2018). The majority of flavones have a hydroxyl group, although they can also be O-glycosylated (Panche et al., 2016; Hostetler, Ralston, & Schwartz, 2017; Joshi et al., 2018). They were shown to be a good alternative for obesity control in a study done in the Netherlands, and it was determined that flavone and catechin consumption was associated with obesity management, reduce the increase in body mass index in women (Hughes et al., 2008). Luteolin, apigenin, tangeretin, baicalein, rhoifolin, diosmetin and tricin flavones from poly-

phenolic flavonoids are found as glucosides and the members of this group are generally obtained from the leaves, flowers and fruits of broccoli, green pepper, rosemary, red pepper, celery, parsley, thyme, carrot, chamomile, mint and onion. In addition, it has been determined that polymethoxyleflavones are also found in citrus peels (Panche et al., 2016; Hostenler et al., 2017; Joshi et al., 2018).

Flavonols

Flavonols are one of the main subclasses of flavonoids, the class in which the C ring is most oxidized. It is quite common in plants and therefore in human diets. Consumption of these compounds is associated with improved biomarkers of cardiometabolic risk (Meneses et al., 2017; Pinto & Santos, 2017). Because they include a 2-phenylbenzo-pyran core with a hydroxyl group at the C-3 position, are also known as 3-hydroxyflavones. At nature, flavonol derivatives with hydroxyl and/or methoxyl groups in different positions are more common (Guliyev, 1999). Flavonols play a variety of important roles, including attracting pollinating insects, influencing color formation, providing UV protection, pathogen resistance, causing interactions between plants and microbe signaling molecules, influencing pollen production, and regulating plant growth (Khalsa, 1999). Furthermore, high levels of phenolic compounds including flavonols, catechins, and anthocyanins have been linked to improved health (Adlercreutz & Mazur, 1997; Dixon, 1999). Foods including onions, garlic, cabbage, leek, cauliflower, broccoli, blueberries, cherries, tomatoes, apples, and red grapes have been discovered as major sources of a category of flavonols that are beneficial to human health.

In plants, quercetin is the most abundant flavonol. Its high concentration in tea is said to give it an astringent flavor. Flavan-3-ols, commonly known as flavanols, have been found in a variety of tea leaves and fruits. While catechin and epicatechin were the most common flavan-3-ols in fruits, epicatechin gallate, gallocatechin, epigallocatechin, and epigallocatechin gallate were the main flavan-3-ols in certain leguminous plants, tea leaves, and seeds (Suzuki, Pervin, Goto, Isemura, & Nakamura, 2016). Many research have been performed on the effects of teas in the prevention and treatment of obesity, diabetes, and cardiovascular illnesses (X. Wang, Ouyang, Liu, & Zhao, 2014; Vinayagam & Xu, 2015; Suzuki et al., 2016). Green tea including epigallocatechin gallate, epigallocatechin (15-18%), epicatechin gallate (5-6%), and epicatechin (2-5%), which accounts for about 68-69% due to its high flavonoid concentration, has emerged as one of the most researched teas (Chen, Zhu, Tsang, & Huang, 2001; S. Wang et al., 2014). The beneficial effects of flavan-3-ols on obesity-related parameters, including reduced body weight, fat mass and cholesterol, were confirmed on the studies performed on mice (Bose et al., 2008; Lee, Kim, & Kim, 2009; Chen et al., 2011; Grove, Sae-Tan, Kennett, & Lambert, 2012; Hoek-van den Hil et al., 2015; Sampath, Rashid, Sang, & Ahmedna, 2017). In an interesting study on mice by Zhang et al. (2019), it was reported that epigallocatechin-3-gallate (EGCG), the major catechin found in green tea, formed an amine metabolite of EGCG in mice and cleared toxic reactive metabolic wastes, thus preventing the development of chronic diseases such as obesity. In the studies conducted by Jansel et al (2016) and Hursel et al. (2009), the importance of a mixture of green tea catechins and caffeine, as a beneficial effect on body-weight management, were reported. In addition, Phung et al. (Phung et al., 2010) reported that in addition to weight loss, this mixture reduced body mass index and waist area. However, obesity-related parameters such as body weight, body mass index, fat mass, and waist and hip circumference have not yielded beneficial outcomes in trials of green tea catechins without coupled with caffeine (Diepvens, Kovacs, Nijs, Vogels, & Westerterp-Plantenga, 2005; Hsu et al., 2008; Jurgens et

al., 2012). Thus, these findings indicated that a synergistic interaction between catechins and caffeine is required to achieve beneficial effects on body weight.

Broccoli (Brassica oleracea L. italica) is a cruciferous vegetable that contains rich flavonols in glycoside form, including kaempferol and quercetin, as well as numerous nutrients (Vallejo, Tomás-Barberán, & Ferreres, 2004; Vasanthi, Mukherjee, & Das, 2009). Thus, broccoli is an excellent functional food (Vallejo et al., 2004; Gliszczyńska-Świgło, Kałużewicz, Lemańska, Knaflewski, & Tyrakowska, 2007; Duan et al., 2021).

Quercetin, which was found to be one of the most active flavonoids in experimental studies, has enabled to have biological activity of many medicinal plants, has been abundant in citrus fruits, in vegetables, red onions, tomatoes and apples (Yamamoto & Oue, 2006; Lesser, Cermak, & Wolffram, 2006; Pinto & Santos, 2017). In the study conducted by Lesser et al. (2006) on pigs, the influences of the dietary fat content on the bioavailability of the flavonol quercetin were investigated, and the enhancement of the bioavailability of the flavonol quercetinse, when administered with a diet containing moderate amounts of fat was reported. Among flavonols, quercetin has been shown to reduce lipid accumulation (Kumazawa, Kawaguchi, & Takimoto, 2006). In the study conducted by Hoek-van den Hil et al. (2015), the effects of quercetin, hesperetin, epicatechin, apigenin and anthocyanins in mice fed were investigated and a high-fat diet was compared with that of normal-fat diet. It was determined that all flavonoids lowered parameters of high-fat induced adiposity, but quercetin was found to be the most effective. In some other studies, in rodents fed, a western or high-fat diet, it was determined that quercetin decreased liver fat accumulation as well as decreased hyperglycemia, hyperinsulinemia, and dyslipidemia (Kobori, Masumoto, Akimoto, & Oike, 2011; Jung, Cho, Ahn, Jeon, & Ha, 2013; Hoek-van den Hil et al., 2015; Imessaoudene et al., 2016; Porras et al., 2017).

Because of having functions of suppressing free radical formation, scavenging free radicals, and regulating or protecting antioxidant systems flavonoids have antioxidant abilities (Wolfe & Liu, 2008; Kumar & Pandey, 2013; Frond et al., 2019; Gu, Howell, Dunshea, and Suleria, 2019) and the 3',4',5'-trihydroxyl group can further increase their effectiveness (Wolfe & Liu, 2008). They inhibit free radical-producing enzymes, decrease lipid peroxidation, and make chelates with metal ions to prevent free radical generation (Leopoldini, Russo, Chiodo, and Toscano, 2006). Flavanols are found in plants that are either monomeric (catechin, epicatechin, epigallocatechin, gallocatechin) or polymeric (proanthocyanidin or dense tannins) forms and have been related to strong antioxidant activity (Frond et al., 2019). In the fermentation of soybeans, cocoa, and tea, microorganisms have been shown to convert flavanols to their free forms. The loss of flavanols during fermentation, on the other hand, usually does not result in a decrease in biological activity (Cho et al., 2011). Flavonols added to the primary components at less than 10% (by weight) have recently been recommended to increase the bioavailability of different secondary components, catechins, such as piperine, rutin, and genistein (Cai et al., 2018).

Flavanones

Flavanones are a subclass of flavonoids (Peterson, Beecher, et al., 2006; Peterson, Dwyer, et al., 2006; Catta-Preta et al., 2012), found in citrus fruits such as oranges, tangerines, grapefruit, and lemons, mainly found as glycosides in citrus fruits, and the most common citrus flavanone glycosides being hesperidin (Salas, Reynoso, Céliz, Daz, & Resnik, 2012).

Flavanones have two main forms, glycons and aglycones linked by a dihydropyrone ring (C), which are a modified flavonoid with a flavan core formed by two aromatic rings (A and B) (Barreca et al.,

2017). They do not have double bonds in the C ring between C2-C3 atoms, as flavones and flavonols do, and due to the asymmetry of the C-2 atom in their structure, they occur in the form of two optical isomers or racemic mixture. In nature usually and particularly in citrus fruits, flavanones are found in the form of glycosylated derivatives.

Naringenin has been shown to have a variety of bioactivities, including antioxidant, anti-inflammatory, hypoglycemic, antihyperlipidemic, and neuroprotective properties (Alam et al., 2014; Mir & Tiku, 2015; Burke et al., 2018). It has been shown in studies to reduce 3% body fat, and reduce blood sugar levels and tolerance, insulin resistance, and LDL levels (Cercato et al., 2021).

Grapefruit flavanones have shown a wide range of health-promoting properties, particularly against heart disease. (Middleton, Kandaswami, & Theoharides, 2000; Mink et al., 2007). Because of its preventive characteristics against coronary heart disease, the American Heart Association has granted many commercially available grapefruit juices the symbol of "healthy heart control"(Cerda, Robbins, Burgin, Baumgartner, & Rice, 1988). Similarly, grapefruit has been shown to have anti-cancer effects in numerous in vitro experiments (Juskiewicz, Zdunczyk, Wroblewska, Oszmianski, & Hernandez, 2002; Vanamala et al., 2006; Murthy, Kim, Vikram, & Patil, 2012).

Plant-derived flavanones are gaining popularity as a result of their potential therapeutic and pharmacological applications (Barreca et al., 2017; George, Dellaire, & Rupasinghe, 2017), and their levels are associated to fruit antioxidant activity. Flavanones are found in a variety of plant components, including flowers, fruits, seeds, and leaves, and play an essential role in plant signaling, defense against UV radiation, microbes and herbivores.

Plant genetics and growth circumstances (production systems and environment) have a big impact on flavonone levels. Despite these health advantages, grapefruit intake is unpopular among people on certain medicines because of the risk of drug interactions (Chebrolu, Jifon, & Patil, 2016).

Anthocyanins

Anthocyanins have a positive charge at the oxygen atom of the C-ring of the flavonoid structure, thus, they are also called flavylium (2-phenylchromenylium) ions, and are found in flowers), fruits, leaves and seeds (Kim, et al., 2012; Inomata, et al., 2013; Trivellini et al., 2014; Gouvêa et al., 2015). They are water-soluble pigments that contribute to the most common colors red, blue, orange, magenta, violet and blue (Koes, Verweij, & Quattrocchio, 2005; Iwashina, 2015). Anthocyanins, which are found in fruits like strawberries, cranberries, raspberries, grapes, and vegetables like red onions, red cabbage, and sweet potatoes, as well as purple-leaf teas (Hsu, Shih, Lin, Chiu, & Lin, 2012), are the chemical components that give them their vibrant color (Marathe, Shah, Bajaj, & Singhal, 2021). There are about 600 different kinds of anthocyanins. Most anthocyanin aglycones are based on anthocyanidins (sugar-free anthocyanins) (Prior & Wu, 2012) such as cyanidin, delphinidin, petunidin, peonidin, pelargonidin, and malvidin, sharing a hydroxylated 2-phenylbenzopyrylium (flavylium) skeleton at the 4', 5, and 7 positions with different substitutions at R1 and R2 (Wang, Rajan, Liu, & Chakrabarty, 2008).

Anthocyanins are classified as an important natural source of valuable phenolic compounds, which are high in grape skins and vacuoles, depending on grape type and degree of maturity (Spigno, Tramelli, & De Faveri, 2007; Hernández-Hierro et al., 2014). They are bioactive compounds that prevent fatigue and aging, as well as having various health benefits such as reducing the risk of coronary heart disease and stroke, ocular diseases, anti-carcinogenic and antioxidant activities, and anti-inflammatory effects and are accepted as nutraceutical, in the food and beverage, pharmaceutical and cosmetic industies (Jiang et

al., 2013; Wallace & Giusti, 2013; Intuyod et al., 2014; Patil & Datar, 2016). One of the most prevalent anthocyanins, cyanidin 3-glucoside, has been shown in studies to lower blood sugar levels and improve insulin sensitivity, as well as to prevent many of the inflammatory effects of obesity (Cercato et al., 2021).

Bioactivity of Flavonoids

In plants, flavonoids, which are responsible for electrical conduction during photosynthesis, are secondary metabolites that play an antioxidant role against the effects of UV rays, and protect against bacterial, fungal, viral pathogens, insects and mammalian herbivores. (Gould & Lister, 2006). A wide variety of in *vivo*-in *vitro* studies have shown the antioxidant, prooxidant, anti-inflammatory, antiviral/bacterial, antidiabetic, cardioprotective, anticancer, and anti-aging effects of flavonoid families (Wang et al., 2018).

The most recently, the dietary phytochemicals have been studied, and their antioxidant activity and anti-cancer usefulness have been demonstrated (Chikara et al., 2018) Furthermore, epidemiological studies have indicated that taking flavonoid-rich foods in sufficient amounts might enhance heart health (Erlund, 2004).

Flavonoid compounds have a wide spectrum of biological activities including antioxidant, anti-inflammatory, antitumor, anticarcinogenic hepatoprotective, antithrombotic and antiviral properties (So et al., 1996; Havsteen, 2002; Crowe et al., 2011; Wedick et al., 2012). Over the past few decades, many relevant epidemiological studies have established that diets rich in plant-derived products help prevent chronic and age-related diseases, including the investigation of flavonoids and their metabolites, among other dietary polyphenols (Schroeter et al., 2002). The active oxygen forms of free radicals (e.g. super oxide anion, hydrogen peroxide and hydroxyl radical), which are by-products of normal metabolism, cause cell function and tissue damage by oxidative stress, during inflammation, and it is known that increased oxidative stress can causes various diseases (Mittal, Siddiqui, Tran, Reddy, & Malik, 2014). As a result of the studies, it was determined that some flavonoids scavenge superoxide, and hydroxyl radicals, and show anti-inflammatory effect by inhibiting the production of the imflammatory mediators. Flavonoids displayed significant antioxidant activity by donating electron, H atom as well as capturing some free radicals. It is their phenolic structure, that enable them to act as hydrogen-donating molecules. It has been determined that flavonoids have cleaning activity due to their phenolic hydrogens (Wang, Wang, Tang, Du, & Li, 2016; Chen, Fan, Wu, Li, & Guo, 2019).

Flavonoids, with their antioxidant capacity and chelating properties (Jucá et al., 2020), have many health-promoting functions such as anticancer activity (Srinivas, 2015), hypolipidemic activity (Wu, 2004), cardioprotective activity (Hodgson & Croft, 2010) and antiviral activity (Del Rio, Borges, & Crozier, 2010). Viruses that cause diseases like SARS, Hepatitis, AIDS, Influenza, Herpes, and others are widespread nowadays, yet some of them (such as SARS-CoV-2) cause global chaos. Because of their antibacterial activity in *vitro*, some flavonoid and isoflavonoid compounds are considered to play a role in plant-microorganism interactions as part of the host plant's defensive arsenal. Although effective treatments are not available for these viral diseases despite all efforts, it has been determined that flavonoids have an effect on viral infection. The mechanisms by which flavonoid phytochemicals act on viruses and inhibit them can be various (Badshah et al., 2021): Flavonoids can bind to the surface proteins of viruses, preventing the virus from binding and entering the host cells (e.g. human cells). Some flavonoids act as a transcription inhibitor and affect the replication process of viruses, some others inhibit the late stages of viral assembly, packaging and release, and by this way conribute to healing. It

is also proposed that flavonoids may also reduce viral load by modulating the immune system (Roschek Jr, Fink, McMichael, Li, & Alberte, 2009; Badshah et al., 2021).

Numerous studies in *vitro* and in animal models of inflammation induced by microbial infections, have found that flavonoids have the potential to inhibit the onset and development of inflammatory diseases (Chen & Nuñez, 2010; Behnia, Sheller, & Menon, 2016). Polyphenolic compounds present in fruits, vegetables, legumes, and cocoa, such as flavonoids, have been shown to have anti-inflammatory effects (Maleki, Crespo & Cabanillas, 2019). Flavonoids have been found to block regulatory enzymes or transcription factors that are crucial for regulating inflammation-related mediators in recent research (Espn, González-Sarras, & Tomás-Barberán, 2017; Xing, Zhang, Qi, Tsao, & Mine, 2019).

Diabetes is one of the most important diseases of our century and is a chronic disease that requires lifelong medical intervention. With hundreds of millions of people suffering worldwide and a rapidly increasing incidence, diabetes places a huge burden on healthcare systems. The effect of flavonoids in the hyperglycemia-induced oxidative stress has been studied. Caco-2 cells were stimulated with high glucose (HG) for 24 hours with and without flavonoids (quercetin, morin, naringenin). Treatment of HG-Caco-2 cells with flavonoids increased cell survival and decreased glucose absorption, indicating that flavonoids protect against hyperglycemia-induced oxidative stress and enhance intestinal barrier functioning via altering underlying intracellular molecular processes (Sharma, Tripathi, Sharma, & Dixit, 2020). In various studies on discovering natural anti-obesity agents, it has been found that plant extract and phenolic components have the potential to inhibit triglyceride absorption (Yun, 2010). In both human and animal studies (in *vitro* and *vivo*), phenolics in olive oil were shown to have beneficial biological activities such as to decrease LDL and triglyceride levels oxidation and increase HDL levels (Cicerale, Conlan, Sinclair & Keast, 2008). It has also been discovered that phenolics have a beneficial impact on the intestinal microbiota by suppressing gene and protein expressions of proinflammatory cytokines involved in cell signaling pathways. (Espn et al., 2017; Xing et al., 2019) Furthermore, these compounds interact with indigestible fibers and their metabolites in the intestinal microbiota, where they synergistically contribute in the low-grade inflammation-metabolic syndrome axis (Burcelin, 2016; Edwards et al., 2017). Recent research has demonstrated that dietary phenolics' functions and health advantages as potent anti-inflammatory agents and efficient immune modulators extend beyond their antioxidant activities (Espn, Gonzalez-Sarras, & Tomas-Barberan, 2017; Xing, Zhang, Qi, Tsao, and Mine, 2019).

Flavonoid Content of Food

Phenolic compounds are initially synthesized in the cytoplasmic surface of endoplasmic reticulum and then transferred to other cell organelles (Fereidoon Shahidi & Yeo, 2016). As intrinsic physiological regulators or chemical messengers, phenolics play a crucial role in plant growth regulation (Cheynier, Comte, Davies, Lattanzio & Martens, 2013). Many foods contain phenolic compounds, including citrus fruits, rosehips, apricots, cherries, grapes, apples, currants, and blueberries, as well as vegetables (onions, green peppers, broccoli, tomatoes, spinach), teas, dark chocolate, coffee beans, and soy products. Furthermore, whole grains are high in phenolic compounds, which are essential sources of dietary fiber and protein (Repo-Carrasco-Valencia, Hellström, Pihlava, & Mattila, 2010). Certain parts of these foods, such as the skin and seeds, are richer in flavonoids than others (Li et al., 2014).

Although phenolic compounds are more or less common in every fruit and vegetable, it is known to be richer in fruits than vegetables (Shahidi & Naczk, 1995). Gallic acid, catechins, and quercetin glucosides are the phenols that are best absorbed by humans (Manach, Scalbert, Morand, Rémésy & Jiménez, 2004).

Flavonoids, which are generally responsible for color, taste, prevention of fat oxidation, protection of vitamins and enzymes (Yao et al., 2004) in foods, also play a decisive role in the nutritional value and sensory quality of foods (Shahidi and Naczk, 1995).

Food processing procedures, such as high heat treatment, storage (Yu & Ahmedna, 2013), and processes such as removing the core and skin portion, can reduce the phenolic content of fruits and vegetables while also limiting their health-promoting properties (Peschel et al., 2006; Capanoglu et al., 2008). Skrede et al. (2000) found that the pulp that comes out of the press after the juice preparation procedure contained around 20% of the anthocyanins in blueberries. Thus, food processing features should be taken into account in order to prevent nutritional losses in the final product during the production process.

In order to further maximize the production of various phenolics in plants, studies are carried out on the phenolic-microorganism interactions in the fermentation system of microorganisms. Recent advances in improving the health benefits of fermented foods are also attracting attention for the food and biotechnology industries. The consumption of phenolic-rich foods is influenced by geography and social habits. The consumption of soybean in the Eastern culture is high in countries such as the United Kingdom, Ireland or Turkey, for example (Shukla et al., 2016; Sanlier, Atik & Atik, 2018). Many Phenol-enriched functional food products have been developed and marketed with clinically proven health benefits The development of a functional food with phenolic compounds, i.e. adding to food, depends on stability, as well as on the sensations in the mouth, such as astringency, bitterness and sourness, which may impair the acceptability of the product by consumers.

The bioaccessibility and bioavailability of phenolic compounds, as well as their physiological effects, are influenced by their potential for release from the food matrix (Carbonell-Capella, Buniowska, Barba, Esteve & Frgola, 2014; Sengul, Surek & Nilufer-Erdil, 2014; Lucas-González et al., 2018). In order to show more absorption in the intestine (Carbonell-Capella et al., 2014) of the amount released from the food matrix and become available for absorption, in vitro models have been developed which has the benefits of being faster, cheaper, and less labor than traditional human nutrition (Kamiloglu, 2019). Digestive enzymes are one of the most important factors determining the bioaccessibility of phenolic compounds (Priyadarshani, 2017). To estimate the bioavailability of various food components (i.e., ascorbic acid, carotenoids, glucosinolates, polyphenols) in vitro models based on human physiology have been developed. The pH, temperature conditions are adjusted and digestive enzymes such as pepsin, pancreatin, lipase, chymotrypsin are used for simulating the conditions of stomach and duodenal digestion stages (Granado-Lorencio et al., 2007; Saura-Calixto, Serrano & Goñi, 2007). Studies have shown that phenolic compounds are extensively metabolized in the intestine and transported to the liver and then to target cells. In addition, phenolic compounds that cannot be absorbed in the intestine have been found to be degraded and reabsorbed by the colonic microbiota (Thilakarathna & Rupasinghe, 2013). The interaction of phenolic compounds with proteins, carbohydrates, lipids and other macromolecules affects their bioaccessibility and bioavailability may protect them against oxidation during their passage through the gastrointestinal tract (Saura-Calixto, 2011). On the contrary, phenol/protein interactions may cause losses in nutritional values due to protein precipitation and enzyme inactivation (Rohn, Petzke, Rawel & Kroll, 2006). Among the phenolics in soluble and insoluble (bound) form in the food matrix, those in insoluble bound form are retained in the matrix through hydrogen bonds or hydrophobic interactions, and have important effects on the binding of cell wall substances and increasing structural stiffness and protecting cells with antibacterial, antifungal and antioxidant activities (Sancho, Bartolomé, Gómez-Cordovés, Williamson, & Faulds, 2001; Liu, 2007). Formation of insoluble (bound) phenolics (ISBP) are the most abundant phenolic acids in commonly consumed vegetables and fruits,

while flavonoids such as catechin, isoquercitrin, quercitrin and quercetin have been found as ISBPs in tropical or subtropical fruits or their leaves. The phenolic acids such as gallic acid, protocatechuic acid, chlorogenic acid, gentisic acid, caffeic acid, vanillic acid, syringic acid, coumaric acid, ferulic acid and cinnamic acid have also been found in various food matrices and abundant in legumes, cereal grains, herbs and other seeds (Kapoor & Dharmesh, 2016).

There have been research on the formation, chemistry, bioaccessibility and bioavailability of soluble and insoluble (bound) phenolics in the food matrix, as well as their potential health effects. In addition to extractable phenolics, insoluble (bound) phenolics are abundant in fruits, notably in the peels and seeds, suggesting that bound phenolics may contribute considerably to the potential for increased health benefits (Luo, Zhang, Li, & Shah, 2016). It has been reported that vegetables and fruits have the most extractable polyphenols or phenolics in soluble free, conjugated forms (Hellstrom & Mattila, 2008), whereas those in insoluble bound form only make up an average of 24% of the total phenolic content in the food matrix (Chu, Sun, Wu & Liu, 2002). Only phenolic acids, namely gallic acid, chlorogenic acid, p-coumaric acid and ferulic acid were found in the ISBP fraction of olive fruit and leaf (Xie, Huang, Zhang & Zhang, 2015). In the ISBP fraction of olive fruit and leaf, only phenolic acids, such as gallic acid, chlorogenic acid, p-coumaric acid, and ferulic acid, were detected (Xie, Huang, Zhang & Zhang, 2015). Although phenolic acid compositions differ significantly between white, red and black rice bran, phenolic acids have been identified as the main fraction ISBP in rice bran (Pang et al., 2018). Studies have also shown that flavonoids can affect the relative concentration of commensal bacteria in the gut, suggesting that dietary flavonoids may act as prebiotic foodstuffs for gut bacteria (Duda-Chodak, Tarko, Satora & Sroka, 2015).

The Role of Flavonoids in Cancer Treatment

Cardiovascular disease, obesity, oxidative stress, glycemia, and cancer are some of the most common causes of death worldwide today. In addition to triggering factors such as chronic infections and obesity in cancer and tumor formation, various environmental risk factors, such as excessively processed foods, high alcohol consumption, tobacco use also indirectly increase the likelihood of cancer (Grivennikov, Greten & Karin, 2010; Moodie et al., 2013; Rauber, Campagnolo, Hoffman & Vitolo, 2015).

The uncontrolled multiplication and spread of normal body cells under the influence of genetic and/or environmental factors is the basis of cancer (Benavente-Garcia & Castillo, 2008). Studies have shown that plants are rich in pharmacologically active compounds that help prevent and treat diseases. The antioxidant potential of a given flavonoid is based on the functional group and its spatial conformation around the nucleus. Flavonoids with a double bond at the C2–C3 and a carbonyl at the C4 position exhibit significant anti-cancer properties (Bailly, 2021). In recent years, studies have suggested that flavonoids obtained from plants have an antioxidant effect or an anticarcinogenic effect through a different mechanism. Flavonoids have primarily been shown to have antioxidant, anti-cancer, anti-inflammatory, and anti-mutagenic effects due to their structure and degree of unsaturation, polymerization, and oxidation of the "C" ring (Diwan, Ninawe & Harke, 2017; Vazhappilly et al., 2019). Flavonoids have been documented in vitro to act as either antioxidants or pro-oxidants, depending on cellular events, dose and bioavailability, while only pro-oxidant effects have been observed and reported in vivo (Procházková et al., 2011; Panieri et al., 2020). One of the antioxidant action mechanisms is the "direct radical scavenging" function, which occurs when the single electrons of a radical become double bonded without

forming another radical, and the other is the "indirect antioxidant mechanism" that occurs with at least 6 different antioxidant mechanisms (Wildman, 2016).

Plant-based natural compounds, especially dietary flavonoids, are important in cancer prevention and to overcome the side effects of conventional cancer treatments, such as radiation and chemotherapy (Gegechkori, Haines, & Lin, 2017; Schirrmacher, 2019). Epidemiological and clinical studies conducted in recent years have shown the existence of a positive effect with a flavonoid-rich diet, on a cardiovascular, neurodegenerative and oncological disorders (Rothwell, Knaze & Zamora-Ros, 2017; Siddiqui et al., 2020). Flavonoids are important as anti-cancer agents and as cytotoxic anti-cancer agents that increase apoctosis in cells (Abotaleb et al., 2019).

As pro-oxidants, flavonoids have protective effect against reactive oxygen species production (Poljsak, Šuput, & Milisav, 2013; Abotaleb et al., 2019) and can inhibit cancer and tumor formation by suppressing the proliferation of cancer cells through p53 (D'Angelo et al., 2017). Diet plays an important role in cancer. For example, high consumption of red and processed meat has been associated with a higher probability of carcinogenesis in humans (Bouvard et al., 2015). Inflammation has a crucial role in cancer's complexity. Various environmental risk factors for cancer development, such as chronic infections, tobacco use, or obesity, are associated with some degree of chronic inflammation. (Grivennikov et al., 2010). Excessively processed food or high alcohol consumption has an impact on the risk of obesity (Moodie et al., 2013; Rauber et al., 2015) and indirectly increases the likelihood of cancer (Grivennikov et al., 2010; Smyth et al., 2015). In contrast, a diet rich in fruits and vegetables for a healthy lifestyle has been associated with a lower risk for different types of cancer (Turati, Rossi, Pelucchi, Levi & La Vecchia, 2015; Aune et al., 2017; van Breda & de Coke, 2018).

Recent studies have shown that flavonoids can inhibit regulatory enzymes or transcription factors that are important for controlling inflammation-related mediators. Numerous in vitro studies and in animal models have determined that flavonoids are potent antioxidants with the potential to inhibit the onset and development of inflammatory diseases. The presence of foods containing flavonol groups, which have biologically important active protective functions, in a daily balanced diet plays an important role in the prevention of cancer (Rothwell et al., 2017; Siddiqui et al., 2020; Panieri et al., 2020).

Cancer, one of the deadliest diseases globally (Basu et al., 2020), is related to the development of oxidative stress causing cell apoptosis (Stone et al., 2014). Although drug resistance, low specificity of antitumor drugs, high cost, undesirable effects on normal cells, biological load of therapy (Siddiqui et al., 2018) are the biggest obstacles in eliminating cancer, this situation has led to the need to design new cytotoxic agents (Chaudhary & Poonia, 2021). Diverse viewpoints on prospective anticancer research, such as combining biochemical and phytochemical components into the design of potent anticancer drugs to produce novel therapeutic candidates, has gained importance. (Ling et al., 2013; Bouyssou et al., 2014; Di Leva et al., 2014). These potential anticancer drugs are expected to inhibit the activity of oncogenic RNAs, promoting tumor suppressive activity. (Calin & Croce, 2006; Wu et al., 2010). Curcumin, a phytochemical component derived from the rhizomes of turmeric (Curcuma longa, haldi), is one of these natural sources and has been used as a spice in Asian foods as well as a medicinal in traditional Indian (Ayurvedic) and Chinese (TCM) medicine for ages (Vyas et al., 2013). It was shown that curcumin-fed mice successfully inhibited lung cancer with significant tumor regression in tumors (Dahmke et al., 2013). Moreover, nanoformulated dendrosomal nano-curcumin has been shown to efficiently suppress glioblastoma cell growth by downregulated pluripotency genes via miR-145 activation (Mirgani et al., 2014), and could be an effective choice for epigenetic therapy of hepatocellular cancer (HCC) (Zamani

et al., 2015). Curcumin and curcumin analogs, florocurcumins, have been shown to improve treatment outcome of patients diagnosed with cancer (Padhye et al., 2009; Ali et al., 2010).

Chalcones are precursors of flavonoids and isoflavonoids that have demonstrated to have stronger anti-proliferative effect than related flavones and flavanones against human liver cancer.

Chalcone derivatives as a new class of drug candidates, designed and synthesized to enhance the biological effects of the 2′-hydroxyflavonone precursor compound against androgen receptor dependent transcriptional stimulation, have been found to have broad-spectrum antiproliferative activity against multiple tumor cell lines, at low micromolar level (Saito et al., 2018).

Lignin is known to have antioxidant properties, thus may be used to control oxidative stress. In colon cancer, which is the populous most common cause of death, studies are being conducted on drugs produced from lignin, by controlling oxidative stress, which comprises a cost-effective, biocompatible, and environmentally friendly nanoparticle carrier functionalized with a ligand for CD44 receptors (Siddiqui et al., 2018).

Flavonoids as Drugs

Thanks to the bioactive compounds it contains, flavonoids, which are part of nutraceuticals and functional foods, are becoming more and more popular worldwide due to the increasing awareness of health protection (Fereidoon Shahidi & Ambigaipalan, 2015) Today, an increasing number of infectious agents are becoming more resistant to commercial antimicrobial compounds. There has been a growing increase in unraveling the mysteries of traditional herbal medicine in the recent decade. As a result of the multidrug resistance and dose-limiting toxicity of the drugs administered to cancer patients, and the positive results of the studies used to help the prevention and treatment of cancer with the anti-cancer properties of flavonoids, it has been a glimmer of hope in the use of flavonoids as drugs (Maleki et al., 2019). The fact that flavonoids are seen as promising candidates for new natural medicines and their potential role in disease prevention and/or therapy requires further research on them (Surajit Das & Chaudhury, 2011). Flavonoids with a low water solubility appear to have limited drug uses (X. Cai, Fang, Dou, Yu & Zhai, 2013). However, recently suitable formulations have been developed to improve and increase the solubility and oral bioavailability of poorly water-soluble flavonoids. It was shown that by adding a polar functional group to the structure of the molecule, reducing the particle size, and by reducing complexation/solubility and improve water solubility, the oral bioavailability and efficacy of drug candidates can be increased (Leuner & Dressman, 2000; Stella & Nti-Addae, 2007; Ghadiri et al., 2018).

Molecular Modeling Applications on Flavonoids

Molecular modeling has become an essential tool for researchers in the drug design process. Modeling provides representation of the three-dimensional structures of molecules and their associated physicochemical properties. It gives researchers better tools to investigate, interpret, explain, and explore phenomena. Molecular modeling is easy to perform using existing software, but the hard part is getting the right model and interpretation (Nadendla, 2004). Furthermore, molecular modeling is crucial for understanding the three-dimensional features of the specificity of drug-receptor interactions at the molecular level. In pharmaceutical research, this field has grown in importance (Cohen, 1996).

The following are studies of molecular modeling applications in this field:

In the study conducted on Epigallocatechin, Kaempferol and Quercetin molecules in 2017, the optimized geometries were obtained at the DFT/B3LYP/6-31G(d,p) level of theory using Gaussian 09 program and by potential energy scan calculations, two local minima of these molecules were found (De Souza et al., 2017).

The molecular properties of two naturally occurring flavonoid compounds mearnsetin and myricetin were calculated using Gaussian 03 W program and DFT/B3LYP/6-311G(d,p) level of theory. The vibration frequency analysis, performed for both neutral and radical species of mearnsetin and myricetin compounds, gave no negative frequency, which proved the obtained structures were real minimum not settle points (Sadasivam & Kumaresan, 2011).

The structure, molecular properties, and antioxidant abilities of three flavonoids (quercetin, hyperin and rutin) were studied at the DFT/B3LYP/6-311G(d) level of theory using Gaussian 03 package program, in a research published in 2014 (Cai et al., 2014).

In the study conducted by Aparicio in 2010, a systematic B3LYP/6-311++G** computational study was conducted using Gaussian 03 program to understand the molecular factors that determine the structural and energetic properties of 17 flavone derivatives in the gas phase. The flavonoids were chosen to reveal the influence of the number and relative positions of the hydroxyl groups on the molecular properties. The strength and topology of intramolecular hydrogen bonds were investigated by calculating the torsion profiles of different conformers for each flavonoid (Aparicio, 2010).

Quantum chemical analysis of the geometries and optoelectronic characteristics of some flavonoids and their derivatives was performed by Kacimi et al (2018), to determine novel molecules, for applications in chemical physics and materials science.

The vibration frequencies of Acacetin (5,7-dihydroxy-4'-methoxyflavone), a flavone compound having anti-cancer and anti-inflammatory properties, were determined using the DFT/B3LYP level of theory and cc-pVDZ and cc-pVTZ basis sets, in a study conducted by Sertbakan et al. in 2016. These calculations were carried with the help of gradient geometry optimization (Sertbakan et al., 2016).

In the study conducted in 2019, calculations based on the DFT/B3LYP/6-311++G(d,p) level of theory, using Gaussian 09 program were made to investigate the molecular structure and spectroscopic properties of kaempferol, a naturally occurring flavonoid molecule. NBO analysis was also performed to reveal the electronic structure of kaempferol (Milenkovic et al., 2019).

Using the Spartan'14 software, the optimal structure of 11 flavonoids with anticancer activity was calculated at the DFT/B3LYP/6-31G* level of theory in a study conducted in 2019. (Erazua et al., 2019).

In a 2007 research, the most stable structures of myricetin and quercetin compounds were computed in the gas phase, including their radicals in the C ring and diradicals in the B ring. Calculations performed using Gaussian 03W program and for neutral molecules in gas phase, DFT/RB3LYP/6-31G (d,p) level of theory was used, whereas for radicals the DFT/UB3LYP/ 6-31G (d,p) level of theory was used. (Elik et al., 2007).

Another study, published in 2016, investigated the hydrogen bond interactions between flavonoids and ethanol/water. Ethanol and water are the most common solvents for extracting flavonoids from propolis. In this study, molecular geometries, hydrogen-bonding energies were calculated at DFT/B3LYP/M062X level of theory with 6-31++G(d,p) basis set by using Gaussian 09 program set (Zheng et al., 2016).

Since the flavonoids have carbonyl and hydroxyl groups they can coordinate metal ions and form complexes and flavonoid metal complexes have many interesting properties (Kasprzak et al. 2015). The structural parameters, HOMO-LUMO energies, electronic structure parameters and electrostatic potential surfaces, of some flavonoids (Quercetin, Luteolin, Myricetin) metal II complexes with Fe+2,

Co+2 and Cu+2, were calculated (Yalcin, 2019) at DFT/B3LYP/6-31++G(d,p) level of theory, using Gaussian 16 program. In this study also natural bond orbital analysis of flavonoid-metal complexes was also performed.

Conformational, structural, magnetic and electronic properties of seven flavonoid structures (flavan, anthocyanidin, flavanone, flavonol, isoflavone, flavone, and flavan-3-ol) having antioxidant activity, were estimated, using Gaussian 09 program, and density functional (de Souza Farias et al., 2021).

CONCLUSION

Flavonoids have received increasing attention in recent years due to their various beneficial properties, including antioxidant, antiflamatuar, hepatoprotective, antimicrobial, antiviral anticancer properties. Nutritional supplements have come to the fore in the field of treatment. More research is needed to elucidate the biological activities of flavonoids, to increase their effects with special functional groups, and thus to meet their therapeutic needs by nutritional sources. In addition to structure-activity-pharmacokinetic effects, it is important to examine mechanisms at the molecular level, especially in flavonoids.

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Chapter 14
Flavonoids: Bioactive Compunds With Anti-Cancer Properties

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ABSTRACT

Flavonoids are a group of over 2000 phenolic compounds with many therapeutic properties. They are based on the flavan (2-phenyl-benzopyran) core and can be found in a free state or as glycosides. Flavonoids are presented in the vegetal world mainly as yellow, but also red, purple, blue, or brown pigments of the petals, leaves, stems, and fruits. This group of bioactive compounds is known for the inhibition of tumors. The chapter summarizes the most important flavonoids with anti-cancer properties, describing their chemical structure, their prevalence among medicinal plants, and their mechanism of action, based on the recent in vivo and in vitro studies.

INTRODUCTION

Flavonoids are a large group of natural phenolic compounds. Their name come from the latin word *flavas*, wich means yellow, as they are found as pigments in the petals, leaves, stems and fruits of the plants.

The chemical structure of flavonoids is based on flavan (3,4-dihydro-2-phenyl-2H-1-benzopyran), or isoflavan (3,4-dihydro-3-phenyl-2H-1-benzopyran), on which different radicals are attached. Flavonoids occur in plants as aglycones or as glycosides (most often *O*-glycosides, but there are also *C*-glycosides).

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Flavonoids have many pharmacological actions, and therefore are widely used for anti-inflammatory, antioxidant, antiallergic, antithrombotic, anti-cancer and anti-proliferative effects. Also, some of them have diuretic, protective, antibacterial, or antifungal action.

Among the flavonoids, some of them show an important inhibition of tumor promotion, as: quercetin, apigenin, kaempferol, luteolin, chrysin, hesperetin, naringenin, jaceosidin, eupatilin, genistein, or daidzenin.

The purpose of the chapter is to analyze in detail the most important flavonoids known for their anti-cancer effects based on the recent studies and their way of action.

BACKGROUND

Plants and their natural compounds are being used for centuries in traditional herbal medicine, but now they are gaining importance in developing new modern drugs, as they are involved in clinical studies for new approaches in human diseases Flavonoids are a large group of natural polyphenolic compounds with interesting pharmacological activities.

Albert Szent-Gyorgyii reported in 1938 the evidence of a pharmacological action for flavonoids, as preventing capillary bleeding and fragility associated with scurvy. Since then, a wide range of pharmacological activities such as anti-inflammatory, antioxidant, antibacterial, antiviral, anticancer, and protective has been discovered for flavonoids (Zakaryan *et al.*, 2017).

Flavonoids act on cancer through a complex mechanism, and their anti-cancer potential is based on the capacity of scavenging ROS, anti-inflammatory action (through different pathways), inhibition of protein kinase activity, of angiogenesis and of cell growth, induction of apoptosis, and suppression of metastasis process.

Kopustinskiene *et al.* (2020) have explained in detail the flavonoids' way of action in cancer. The authors reported that″ flavonoids exert a wide variety of anticancer effects: they modulate reactive oxygen species (ROS) - scavenging enzyme activities, participate in arresting the cell cycle, induce apoptosis, autophagy, and suppress cancer cell proliferation and invasiveness″. Moreover, flavonoids ″target apoptotic signaling cascade both extrinsic, related to tumor necrosis factor (TNF) superfamily with main signaling protein—caspase 8; and intrinsic—mitochondrial pathway, where Bcl-2 family proteins launch the activation of caspases 9, 3 and 7, stimulating the cell death pathways″ (Kopustinskiene *et al.*, 2020).

Benavente -Garcia & Castillo (2008) have described flavonoids as inhibitors, preventing the formation of cancer cells; as blocking agents involved in reaching critical initiation sites, and as transformation agents, influencing the metabolism of carcinogenic components. Some of the flavonoids may ″induce the expression of different tumor suppressor genes that may contribute to decreasing cancer progression and metastasis″. (Selvakumar *et al.*, 2020).

FLAVONOIDS WITH ANTI-CANCER PROPERTIES

Chemical Structure of Flavonoids

Flavonoids are polyphenolic compounds with 15 carbon atoms with two aromatic rings (A, B) connected by a bridge with three carbon atoms (C). Flavonoids can be divided into different sub-groups based on the position at which the B ring is attached to the C ring, and the oxidation status and the degree of

saturation of the heterocyclic ring. One distinctive sub-group of flavonoids is isoflavone, which has the B ring attached at position 3 on the C ring. Those in which the B ring is linked in position 2 can be subdivided in: flavones, flavonols, flavanones, and anthocyanidins (Figure 1).

Flavones are structurally characterized by the presence of unsaturated C ring at C2 - C3, unhydroxylated at C3 and the presence of the ketone group at C4. Flavones are found in plants in the form of O-glycosides and C-glycosides. Food flavones are usually the glycosides of apigenin and luteolin, which have been detected in celery, parsley, and other plants. Many flavones appear as 7-O-glycosides, but there are also apigenin-8-C-glucoside (vitexin), apigenin-6-C-glucoside (isovitexin), or luteolin-8-C-glucoside (orientin) (Clifford & Crozier, 2011).

Flavonols occur widely throughout the plant kingdom and possess an unsaturated C ring in the C2 - C3 position, which is usually hydroxylated at C3 and oxidized at C4. The main flavonols are quercetin and kaempferol, isorhamnetin followed by myricetin, fisetin and galangin. The presence of the –OH group in flavonols has an important role in determining their biological activity. The most common flavonols (kaempferol, quercetin, isorhamnetin) are usually found as glycosides at positions 5, 7, 3 ′, 4 ′ and 5′.

Flavanols exist both in the form of monomers (catechins) and in the form of polymers (proanthocyanidins). Catechin and epicatechin are the main fruit flavanols, while galocatechin, epigallocatechin and epigallocatechin gallate, are found in certain legumes, in grapes and in tea. Unlike other classes of flavonoids, flavanols are not glycosylated in food.

Flavanones are structurally characterized by the saturated chain between C 2 and C3 and the presence of the oxygen atom in the C4 position. They are usually glycosidized compounds with disaccharide in the C7 position. These compounds are present in tomatoes and herbs such as mint and abound in *Citrus* fruits. Some of the best characterized flavanones are naringenin and hesperetin. Naringenin is well known for its ability to affect drug metabolism.

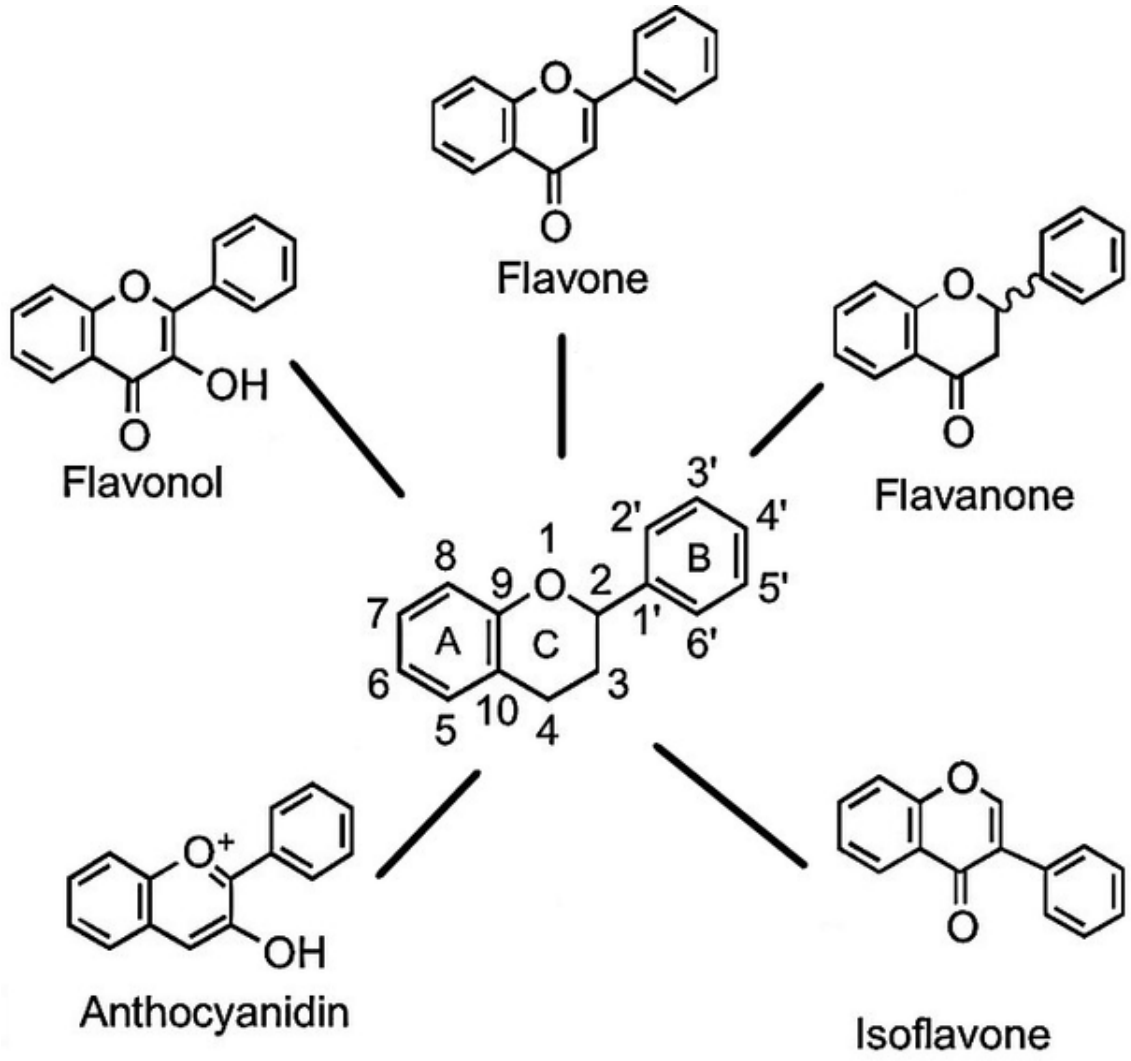
Isoflavones are derived from 3 phenyl chromane. Isoflavones such as genistein, daidzein and cumestan derivatives develop estrogenic properties due to their estrogen-like structure. Although they are not steroids, they have hydroxyl groups in a configuration analogous to that of the hydroxyls in the estradiol molecule. This gives them the ability to bind to estrogen receptors and, therefore, are also called phytoestrogens. Isoflavones are found almost exclusively in legumes, as soybeans. Isoflavones are found in 4 forms: aglycones, 7-O-glucoside, 6 "-O-acetyl-7-O-glucoside, and 6" -O-malonyl-7-O-glucoside (Manach *et al.*, 2004).

Prevalence of Flavonoids in Plants

Flavonoids are distributed mainly in Angiosperms, but can be found occasionally in Gymnosperms, Pteridophytes and Bryophites. They abound in families as *Apiaceae*, *Asteraceae*, *Fabaceae*, *Lamiaceae*, *Liliaceae*, *Malvaceae*, *Polygonaceae*, *Rosaceae*, *Rutaceae*, or *Scrophulariaceae*, where their diversity is maximum. The main sources of flavonoids for human diet are fruits and vegetables, as well as beverages like green, black tea, or wine.

Flavonoids are secondary metabolites of the plants. Their biological role is to assist cellular respiration, as coenzymes in metabolic reactions and growth regulators, to help in combating oxidative stress, and to ensure the protection of tissues against UV radiation. Glycosides are located inside the vacuoles, in the epidermis or mesophyll of the leaves, while aglycones, are distributed among lignified tissues, as the cuticle of the leaves, fibers, and phloem or xylem bundles.

Figure 1. Chemical structure of the main classes of flavonoids



Flavonoids with Anti-Cancer Properties

Quercetin

Quercetin (3,3 ‘, 4’, 5,7-pentahydroxyflavone) is a polyphenolic flavonoid widely distributed in fruits and vegetables, as apples, onion, plants from *Brassicaceae* family, green tea, and other plants as *Hypericum perforatum* L., *Ginko biloba* L., *Sambucus candensis* L., etc.

Quercetin is found both as aglycone and glycosilated form in nature and is the most studied flavone for its pharmacological actions that include antioxidant, anti-inflammatory, protective, antiallergic, antiviral, and anti-cancer properties.

Quercetin modulates the growth of many cancers cell lines by blocking the cell cycle, tumor cell proliferation and by inducing apoptosis.

The antioxidant mechanism of quercetin is manifested at cellular concentrations that can be obtained through diet (Egert *et al.*, 2008), while in higher concentrations, it causes pro-oxidant action, manifested by depletion of glutathione which is beneficial to initiate apoptosis in tumor cells (Metodiewa, 1999; Awad *et al.*, 2000). The anti-cancer effects of quercetin include its ability to promote loss of cell viability, apoptosis, and autophagy by modulating the PI3K / Akt / mTOR, Wnt / β-catenin and MAPK / ERK1 / 2 pathways. Zheng *et al.* (2019), stated that quercetin induced the inhibition of cancer cell growth by apoptosis, the molecular mechanism being related to the reduction of Bcl-2 gene expression and the increase of the apoptosis regulatory gene expression, Bax. The autors emphasize that quercetin "systematically modifies PI3K, MAPK, and WNT pathways by modulating the expression of several proteins that lead to inhibition of cell proliferation, DNA damage, and apoptosis" (Sundaram *et al.*, 2019). In an *in vivo* model, quercetin significantly decreased tumor volume by substantially reducing AMPK activity. In addition, similarly, by inhibiting AMPK in a cell culture system, quercetin-induced apoptosis was more pronounced in hypoxic conditions than in normoxic conditions (Kim *et al.*, 2012). The effect of quercetin in inhibiting cell proliferation was associated with cell cycle stop in the G2 / M phase. In another study, quercetin can exert its anticancer effects by inhibiting topoisomerase I / II DNA, cytochrome c release, capsase 3 activation, NF-κB activation (Mu *et al.*, 2007), inhibition of VEGFR-2 phosphorylation, m-TOR, AKT and enzyme ribosomal S6 kinase, with a role in angiogenesis (Pratheeshkumar *et al.*, 2012).

Many *in vitro* and *in vivo* studies have suggested that quercetin exerts beneficial anti-carcinogenic effects in various types of cancer: lung, breast, prostate, gastric, cervical, and uterine cancer (Zeng *et al*., 2012; Klimaszewska-Wiśniewska. *et al.*, 2017; Rannganathan, *et al.*, 2015; Wang *et al*., 2011; Yamada *et al.*, 2020; Kedhari *et al*., 2019; Yang *et al.,* 2015).

Apigenin

Apigenin (4′, 5, 7- trihydroxyflavone) is abundant in many plants, including fruits and vegetables, especially from the *Apiaceae* family. It occurs as aglycone, as apigenin-7-*O*-glucoside and various acylated derivatives.The species with the highest concentrations of apigenin are *Petroselinum crispum* L., *Apium graveolens* L., *Coriandrum sativum* L., *Matricaria chamomilla* L., *Achilea millefolium* L., *Origanum vulgare* L*., Ocimum basilicum* L., *Camelia sinensis* L., *Mentha spicata* L., *Citrus* sp*., Echinacea* ssp., *Ginkgo biloba* L. and *Glycylrrhiza glabra* L. The maximum quantity of apigenin (at 45,035 μg/g) has been reported in dried parsley (Shankar *et al.*, 2017).

The recent studies showed antioxidant, anti-inflammatory, immunomodulatory, antispastic and anti-carcinogenic properties for apigenin.

Apigenin exert different anti-inflammatory pathways, including p38/ mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase Akt, as well as prevent the degradation and translocation of the nuclear factor-kappaB (NF-κB), and reduce COX-2 activity. It also reduces the production of pro-inflammatory citokines as tumor necrosis factor (TNF-α), and interleukine IL-6. (Huang *et al.*, 2010, Lee, 2007).

As Seo *et al.* (2014) noticed, ″apigenin can regulate intrinsic apoptotic pathways, changing mitochondrial membrane potential and causing the release of cytochrome C in the cytoplasm, which subsequently activates caspase 3, and turns on apoptosis″. Salehi *et al.* (2019) showed apigenin induces apoptosis through modulating proteins expression. At the molecular level, apigenin inhibits several protein-tyrosine and serine- kinases including MAPK, PI3K-Akt, Src kinase, casein kinase 2, cell cycle regulated kinases, JAK kinases, and thus affecting IGF-growth axis, NF-κB, Stat-3, and p53 (Sung *et al.*, 2016). Apigenin

acts on the cell cycle by arresting G2/M and G0/G1 phases due to inhibition of p34, and in addition, it promotes apoptosis by releasing of cytochrome c and induction of apoptotic protease activating factor 1 (Apaf-1), which ultimately determines caspase activation and poly (ADP-ribose) polymerase (PARP)-cleavage (Shukla & Gupta, 2004).

Apigenin had the potential to inhibit hormone-related cancers as prostate, breast, cervical, ovarian, adrenal, and thyroid cancer. It has also inhibited tumor cell invasion and metastases in colon, gastric, lung, liver, skin, hematologic cancer, and neuroblastoma, with promising results (Shukla & Gupta, 2004; Seo *et al*., 2014; Liu.*et al.,* 2021; Shukla *et al.,* 2015; Zhang *et al.,* 2015).

Kaempferol

Kaempferol (3,4′,5,7-tetrahydroxyflavone) is a flavonoid found in many edible plants (tea, broccoli, cabbage, beans, endives, leeks, tomatoes), but also in medicinal plants, including *Equisetum spp, Sophora japonica, Ginkgo biloba, Tilia spp,* and propolis. Due to its lipophilic character, kaempferol is absorbed in the small intestine by passive diffusion and active transport but has a very low oral bioavailability (Alam *et al.*, 2020). Epidemiological studies suggest that a high intake of kaempferol is associated with a lower risk of cancer (Dang *et al.*, 2015; Garcia -Closas *et al.*, 1999; Gates *et al.*, 2007; Nothlings *et al.*, 2007).

Kaempferol has antioxidant potential and reduce the free radicals and ROS (Kampkotter *et al.*, 2007; Verma *et al.,* 2009).

Kaempferol induces anticancer effects mainly by downregulating the expression of proteins involved in cancer formation along with inducing apoptosis, stopping the cell cycle, inhibiting angiogenesis, and increasing the sensitivity of cells to anti-cancer drugs. In cancer cell cultures, kaempferol induced apoptosis both extrinsically and intrinsically. Thus, kaempferol has been shown to alter the expression of several Bcl-2 proteins, leading to depolarization of the mitochondrial membrane, release of cytochrome c, and activation of caspase-3. In addition, kaempferol increases FAS-L expression, increases caspase-8 activity causes Bid cleavage and caspase-3 activation. Kaempferol inhibit cancer cell proliferation by activating MEK-MAPK, inhibiting ERK, down-regulating bcl2 expression (Li *et al.*, 2017, Mishra *et al.*, 2018; Zhu & Xue, 2019), through activating death receptors and the mitochondrial pathway, or by decreasing the expression of vascular endothelial growth factor (VEGF) and inhibiting TGF-β1 induced by EMT (Luo *et al.*, 2009, Huang *et al.*, 2010). Huang *et al.* (2013) previously reported that kaempferol can induce inhibitory effects by stopping the G2 / M phase cell cycle and autophagy. These could be the result of modulation of CDK1 / cyclin B expression and AMPK and AKT signaling pathways. As an inverse agonist for estrogen-associated alpha and gamma receptors (ERRalpha and ERRgamma), kaempferol can increase apoptosis of cancer cells by the PI3K-Akt signaling pathway and the hTERT and ErbB signaling pathway (Kashafi *et al.*., 2017, Wang *et al.*, 2009, Lee & Kim, 2016). In addition, studies have confirmed that kaempferol can induce cell cycle arrest and inhibit G1 / S cell cycle transition (Yoo *et al.*, 2015, Zhu & Xue, 2019), and may inhibit cell proliferation by suppressing ESR1 levels and inhibiting SRC (Lee *et al.,* 2018).

In vitro and i*n vivo* studies have suggested that kaempferol exerts beneficial anti-carcinogenic effects in various types of cancer: hepatic, colon, lung, breast, cervical (Zhu. *et al.*, 2021; Lee *et al*., 2014; Lee *et al*., 2018; Zhu, Le *et.al,* 2019; Kashafi, E *et al.,* 2017; Jo *et al.*, 2015).

Luteolin

Luteolin is 3',4',5,7-tetrahydroxyflavone, a natural compound that is present in many medicinal, alimentary or condimental plants, often found in many glycosylated forms. The main sources of luteolin are celery, parsley, broccoli, onion leaves, green chili, beans, radishes, carrots, peppers, cabbages, apple skins, and chrysanthemum flowers (Miean & Mohamed, 2001).

Among the biological effects of luteolin are antioxidant, anti-inflammation, anti-allergy, anticancer and hormonal.

Luteolin's anti-cancer mechanism of action is associated with induction of apoptosis, suppressing cell survival signaling, anti-angiogenesis, and anti-metastasis.

It has been demonstrated that luteolin can interfere with both the extrinsic and intrinsic apoptosis pathways. In the intrinsic pathway, luteolin act by increasing of DR5, due to activated transcription of the *dr5* gene, which leads to sequential activation of caspase-8, caspase-10, caspaze-9, and caspaze-3, and of Bcl-2-interacting domain cleavage (BID) (Horinaka *et al.*, 2005). Activating the intrinsic pathway of apoptosis by luteolin is realised through DNA damaging by inhibiting DNA topoisomerases and activating p53 (Shi *et al.*, 2007).

Luteolin can supress cell survival signaling through blocking of NF-κB, converting TNFα from a tumor promoter to a tumor suppressor, and by inhibiting Bcl2 family members. It is a potent agionesis inhibitor wich acts through decreasing of vascular endothelial growth factor (VEGF) secretion due to inhibition of hypoxia-inducible factor-1α (HIF-1α) through p53-mediated proteasomal degradation, as well as by supressing of hyaluronidase and maintaining the neovascularization barrier (Hasebe *et al.*, 2003;Kupussamy *et al.*, 1990).

Anti-metastasis effect of luteolin is linked with its capacity of suppressing production and secretion of cytokines (TNFα and IL-6) that can stimulate cancer cell migration.

The chemoprevention properties of luteolin are since it blocks the formation and activation of the carcinogenic agents from processed food, intensifies detoxification processes and stimulates DNA repair (Taj *et al.*, 1996).

In vivo and *in vitro* studies showed that luteolin suppressed growth of tumors formed from human skin carcinoma, leukemia, hepatoma, colon prostate and ovarian cancer cells (Cheng *et al.*, 2005; Lee *et al.*, 2005; Lim *et al.*, 2007; Fang *et al.*, 2007; Samy *et al.*, 2006; Byun *et al.*, 2010; Seo *et al.,* 2017; Wang *et al.,* 2018; Potočnjak *et al.,* 2020).

Chrysin

Chrysin, (5,7-dihydroxyflavone), a flavonoid from different medicinal plants, as *Artemisia mandshurica*, Passiflora *caerulea, Passiflora incarnata, Oroxylum indicum*, honey and propolis, presents a variety of bioactivities, such as antioxidant, anti-inflammatory and anti-cancer.

Sun *et al.* (2012) examined the anticancer properties of chrysin and reported that it has anti-HDAC8 activity and can inhibit chromatin remodeling in breast cancer cells. Chrysin was found to inhibit cell proliferation by blocking the cell cycle in the G1 phase, down-regulating HDAC-2, 3 and 8, and decreasing the degree of H3me2K9 methylation. In addition, chrysin regulates apoptosis-related p21 protein expression by protein methylation and hyperacetylation, an important factor leading to cell apoptosis (Pal-Bhadra *et al.*, 2012).

Chrysin showed chemopreventive effects in colorectal cancer cells, mainly due to the death of TNF-mediated apoptotic cells, and the aryl hydrocarbon receptor, a transcription factor, appeared to modulate this process (Ronnekleiv-Kelly *et al.*, 2016; Bahadori *et al*., 2016). In addition, in human triple-negative breast cancer cells, treatment with chrysin inhibited dose-dependent potential of cancer cells for invasion and migration by downregulation of MMP-10, EMT, and the pathway. PI3K / Akt signaling (Yang *et al.*, 2014; Sean *et al.,* 2016; Kim *et al.,* 2020) observed that chrysin treatment of cancer cell lines induced Tnfα and Tnfβ gene expression and activated several TNF-mediated signaling pathways, with findings suggesting that TNF-mediated apoptosis underlies the anticancer effects of chrysin.

Hesperetin

Hesperetin (3',5,7-trihydroxy-4'-methoxyflavanone) is a flavanone present as a major compound in most *Citrus* species, being abundant in oranges, grapefruits and lemons. It occurs as aglycone, but mainly in the form of glycoside hesperidin.

It has been known for its vitamin-like effect because it decreases capillary permeability (vitamin P), leakiness, and fragility, and has been used in various peripheral circulation disorders (Parhiz *et al.*, 2005). Hesperetin has important antioxidant, anti-inflammatory, protective and anti-cancer properties.

It acts in cancer through different mechanisms involved in the signaling pathways, by promoting mitochondrial apoptosis, and affecting the intracellular ROS. Roohbakhsh *et al.* (2015) noticed that hesperetin reduce tumor growth by targeting multiple cellular protein targets as caspases, B-cell lymphoma 2 (Bcl-2) and Bcl-2 associated X protein (Bax). Ferreira de Oliveira *et al.* (2019) reported that hesperetin caused increased levels of p53 and cyclin-dependent kinase inhibitors, which leads to cycle cell arrest. In addition, its apoptotic actions are due to altered ratios of pro-/antiapoptotic proteins, caspase activation JNK pathway activation and caspase-independent pathways. Moreover, Li *et al.* (2019), found that hesperetin can inhibit PI3K/ AKT signaling pathway by upregulating the expression of PTEN. Zarebczan *et al.* (2011) also discovered that hesperetin is a potential Notch1 activator that is involved in carcinoid tumor suppression.

Many *in vivo* and *in vitro* studies shown that hesperetin can inhibit the growing of many types of cancer, as prostate cancer, cervical cancer, breast cancer, glioblastoma, esophageal cancer, non-smll cell lung cancer, lung cancer, pancreatic cancer, gastric cancer, and hepatic cancer (Wu *et al.*, 2016; Ersoz *et al.*, 2019; Li *et al.*, 2020; Lee *et al.*, 2019; He *et al.*, 2020; Kong *et al.*, 2020).

Hesperetin has a low water solubility which requires the use of solubilizing agents for oral administration. Wolfram *et al.* (2016) have developed a biocompatible liposome-based delivery system for hesperetin with therapeutic efficacy proved on lung and breast cancer cells as an alternative for future clinical use of this compound for cancer therapy (Wolfram *et al.*, 2006).

Naringenin

Naringenin (4,5,7-trihydroxy-flavanone) is a flavanone found mainly in *Citrus* fruits juice, as grapefruit, orange, and lemon. Kanaze *et al.* (2007) studied the pharmacokinetics of naringenin and concluded that after oral administration, naringenin is rapidly absorbed, followed by accumulation in plasma and then cleansed mainly through kidneys.

It has many pharmacological effects, as antioxidant, anti-inflammatory, protective, anti-diabetic, and anti-cancer, for which it was included in many recent studies.

Zhao *et al.* (2019) reported that naringenin may inhibit cell proliferation in association with with cell cycle arrest at the G0/G1 phase, and additionally promote apoptosis and deposition at the sub-G1 phase. It was noticed that naringenin arrests the cell cycle at the G2 phase and induces apoptosis by interfering with caspase-3 and caspase-9 activity (Wang *et al.*, 2019). In an *in vitro* study on prostate cancer cells, Lim *et al.* (2017) showed that naringenin stopped proliferation and migration, promoted apoptosis and ROS production, and decreased mitochondrial membrane potential, which led to increased Bax and decreased Bcl-2 proteins. Naringenin also reduced phosphorylation of ERK1/2, and P38. A more recent study emphasized that naringenin can also reduce the expression of MMP-2 and MMP-9 and increase expression of caspase 3 (Shi *et al.*, 2021). Additionally, naringenin can inhibit angiogenesis, through inhibiting endothelial cell proliferation, survival, migration, and capillary-like structures (tube) formation and reduced neovascularization (Li *et al.*, 2016; Choi *et al.*, 2020).

Naringenin showed an effective action on many types of cancer, as skin, breast, prostate, lung, cervix, colorectal, pancreatic, placental, gastric, bladder and colon cancer, choriocarcinoma, melanoma, and glioblastoma (Li *et al.*, 2014; Liao *et al.*, 2014; Song *et al.*, 2016; Zhang *et al.*, 2015; Zhang *et al.*, 2016; Lim *et al.*, 2017; Lian *et al.*, 2018; Park *et al.*, 2018; Zaim et al., 2018; Chen *et al.*, 2019; Akhter *et al.*, 2020; Kumar *et al.*, 2020; Shi *et al.*, 2021).

To improve the bioavailability of this flavanone there were developed many pharmaceutical derivates of naringenin that have an improved efficacy: nanoparticles, nano-emulsions, cyclic combinations, and others.

Jaceosidin

Jaceosidin (4′, 5, 7-trihydroxy-3′, 6-dimethoxyflavone) is a methoxylated flavone found as a major compound of the medicinal plants of *Artemisia* genus. It has anticancer, anti-oxidative, anti-inflammatory, antiallergic, antibacterial and immunosuppressive effects.

The anticancer mechanism of jaceosidin involves selective suppression of proliferation and accumulation of cells at the sub-G1 stage of the cell cycle, together with the increased cleavage of caspase-9 and caspase-3 (Han *et al.*, 2018). Khan *et al.* (2011) has showed that the ″G2/M phase arrest is associated also with DNA fragmentation, up-regulation of p53 and p21 and subsequent down-regulation of cyclin B1 and CDK1 expression at mRNA as well as at protein level″ (Khan *et al.*, 2011), while Lv *et al.* (2008) noticed that jaceosidin induces apoptosis through activating caspase-3 via mitochondrial pathway. In a recent study on breast cell lines, Ojulary *et al.* (2020) observed that ″jaceosidin similarly modulated the expressions of apoptosis-associated proteins and revealing a coaction between Bax and Bcl-2, striking a balance between cell survival/cell deaths″. Moreover, jaceosidin may attenuate upregulation of COX-2 and of MMP-9, by blocking extracellular signal-regulated ERK-1 and ERK-2 phosphorylation (Jeong *et al.*, 2007). Additionally, Lee *et al.* (2005) showed that ″jaceosidin inhibited binding between the E7 oncoprotein and the Rb tumor suppressor protein and inhibited the function of HPV-16 harboring cervical cancer cells″ (Lee *et al.*, 2005).

The antioxidant effect of jaceodidin has an important role in the antitumor action, and it consists in inhibiting ROS that are involved in regulation of NF-kappaB signaling and deceasing of COX-2.

Jaceosidin was found to suppress growing different cancer cell lines, as glioblastoma, squamous cell carcinoma, cervical cancer, ovary cancer, oral cancer, and breast cancer (Nageen *et al.*, 2021).

Eupatilin

Eupatilin (5,7-dihydroxy-3',4',6-trimethoxyflavone) is a bioactive flavone from some *Artemisia* genus plants, widely used in traditional Asian medicine. It has antioxidant and anti-inflammatory properties, for which is used in gastritis and peptic ulcers, for mucosal protection (Oh *et al.,* 2005).

Recently it has been shown that eupatilin has anti-cancer effects. Cheong *et al.*, (2011) noticed that ″eupatilin inhibits angiogenesis in gastric cancer cells by blocking the expression of signal transducer and activator of transcription 3, and the expression of vascular endothelial growth factor (VEGF)″ (Cheong *et al.*, 2011). Eupatilin can also act in human endometrial cancer cells by arrest ing the cell cycle at the G2/M phase through upregulation of p21 (Cho *et al.*, 2011). Furthermore, Wang *et al.,* (2016) reported that eupatilin has an anticancer effect on glioma cells with a mechanism that involve the inhibition of cell viability, decreased migration and proliferation, and increased apoptosis of tumor cells. It was found that eupatilin can suppress some transmembrane receptor expression, important for the proliferation and invasion of tumor cells (Notch-1) (Wang *et al.*, 2016). Eupatilin also significantly inhibited renal carcinoma cells, as Zhong *et al.* (2019) reported, by downregulating microRNA-21 through the activation of yes-associated-protein-1 (YAP1), which mediated the proapoptotic and antimigratory effects.

Genistein

Genistein- (4′,5,7-trihydroxyisoflavone) belongs to the class of isoflavonoids and is a typical example of a phytoestrogenic compound. It appears as main, secondary metabolite of the species *Trifolium*, *Glycine max* L., and *Genista sp*.

Genistein acts as a chemotherapeutic agent against various types of cancer, mainly by altering apoptosis, cell cycle, angiogenesis and inhibiting metastases. Several reports have shown that genistein can induce cell cycle arrest and can modulate regulatory proteins of the cell (Ramos, 2007). Gu *et al.*, (2005, 2009) observed that genistein significantly inhibited the growth of cancer cells, leading to the cessation of the G2 / M cell cycle and a significant decrease in S phase. In this study, a significant reduction in p125FAK was observed, suggesting that genistein may serve as an anticancer agent by blocking the FAK signaling process, which plays a crucial role in angiogenesis and apoptosis (Gu *et al.*, 2005, 2009). Several other studies have described the ability of genistein to induce cell cycle inhibition by arresting proteins at the G2 / M control point through combined effects on CdC2, cyclin B1, and other cell cycle proteins, which result in decreased cancer cell proliferation (Choi *et al.*, 1998; Ae Park *et al.*, 2006). Moreover, genistein promotes noninvasive effects by suppressing MMP-9 transcription by inhibiting the activity of activating protein (AP) -1 and nuclear factor-k B (NF-κB) (Wang *et al.*, 2014). Genistein can inhibit tumor angiogenesis by suppressing VEGF-mediated signaling pathways (Guo *et al.*, 2007). It also inhibits the expression or secretion of other angiogenic factors such as PDGF-A, TF, and the enzymes uPA, MMP-2 and MMP-9, and in contrast, upregulates the expression of angiogenesis inhibitors PAI-1, angiostatin, endostatin and TSP-1 (Su *et al.*, 2005). Genistein has been observed to downregulate genes related to cell adhesion (eg, VE-cadherin, αV integrin, connexin 43, and multimerin) to mRNA (Piao *et al.*, 2006). Therefore, these studies demonstrate that genistein can inhibit the growing of tumors and reduces the formation of metastases in a variety of cancer types, as gastric, colorectal, lung, liver, prostate, and breast cancer (Spagnuolo *et al.*, 2015).

Daidzenin.

Daidzein (7-hydroxy-3- (4-hydroxyphenyl) -4H-chromen-4-one) is an isoflavone found in soy and other legumes. It has been reported that daidzein has several bioactivities, including antitumor.

He *et al.* (2016) reported that daidzein reduced cell viability in a time- and concentration-dependent manner, causing G1 / S cell cycle arrest and bladder cancer cell apoptosis. Mechanism studies have shown significant regulation of the FGFR3 signaling pathway, with phosphorylation levels of FGFR3, Akt and Erk proteins being inhibited under daidzein treatment. Another study showed that daidzein is effective in reducing the number of human breast cancer cells by inhibiting growth and apoptosis. Furthermore, daidzein-induced apoptosis has been shown to be initiated by the ROS, downregulation of Bcl-2 and up-regulation of Bax, leading to the release of cytochrome C from mitochondria and on caspase-9 and caspase-7 activation and, finally, on cell death (Jin *et al.*, 2010). Guo *et al.*, (2020) showed that daidzein inhibits dose-dependent proliferation and colony formation of lung cancer cells by reducing the levels of IL6 and IL-8. In addition, daidzein decreased the expression and activation of p65-NFκB, Ki-67 and p65-NF-κB levels in tumors.

Some of the mechanisms of flavonoids actions revealed by *in vitro* and *in vivo* tests are summarized in the Table I.

FUTURE RESEARCH DIRECTIONS

It is recommended that researchers should work on exploring the mechanism of action of these natural potent anti-cancer compounds, through *in vitro* and *in vivo* studies, and to extend their research on other types of cancer cells.

CONCLUSION

Based on recent studies, flavonoids are important natural compounds with anti-cancer effects. They act by activating the apoptosis and arresting cell cycle. Also, flavonoids can suppress angiogenesis and stop the proliferation of tumor cell through metastasis. Some of them have chemopreventive action, too. In conclusion, flavonoids can be used as promising natural anti-cancer treatments, as scientific data suggest.

Table 1. Some of the characteristics of the anticancer flavonoids

Flavonoids	Type of cancer	Tests	Mechanism of action	Authors
Quercetin	• Lung cancer • Breast cancer • Gastric cancer • Hepatic cancer • Cervical cancer • Prostate cancer	• *In vitro* tests on A-549 lung cancer cells and *in vivo* xenograft mice studies • *In vitro* A 549 non-small lung cancer cells • *In vitro* tests on cell lines (MCF-7 and MDA-MB-231) • *In vitro* cell lines AGS (ATCC, CRL-1739) and MKN28 (JCRB, 0253) tests • *In vitro* HuH7 hepatic cancer cells study • *In vitro* HeLa cervical cancer cells test • *In vitro* test on PC-3 and LNCaP cells and *in vivo* xenograft tumors in male mice	• Apoptosis by regulation bcl-2 and bax gene • BCL2/BAX-mediated apoptosis • Apoptosis by suppression via p38MAPK pathway • Activating the mitochondria pathway • Suppressed HGF- and TGF-α-induced migration •Alters the PI3K, MAPK and WNT pathways • Inhibited angiogenesis by TSP-1 upregulation	• Zheng *et al*., 2012 • Klimaszewska-Wiśniewska *et al.*, 2017 •Ranganathan, *et al.*, 2015 • Wang *et al*., 2011 •Yamada *et.al.*, 2020 • Sundaram *et al*., 2019 •Yang *et al,* 2015
• Apigenin	• Breast cancer • Ovarian cancer • Prostate cancer • Thyroid cancer	• *In vitro* MDA-MB-453 breast cancer cells test • *In vitro* human ovarian cancer cell lines tets • *In vitro* test on human prostate cancer PC-3 and 22Rv1 cells, *in vivo* test with xenograft tumors in male mice • *In vitro* BCPAP cancer cell line	• Induction of caspase-dependent apoptosis by inhibiting STAT3 signaling • Downregulating ER-mediated PI3K/AKT/mTOR expression • inhibition of p-IKKα, NF-κB/p65, proliferating cell nuclear antigen and increase in cleaved caspase 3 expression • arresting of cells in the G2/M phase via down-regulation of Cdc25C expression, autophagy by Beclin-1 accumulation	• Seo, *et al*., 2014 • Liu.*et al.,* 2021 • Shukla & Gupta, 2015 • Zhang *et al.,* 2015
•Kaempferol	• Hepatic cancer • Breast cancer • Cervical cancer	• *In vitro* HepG2 liver cancer cells test • *In vitro* triple-negative breast cancer (TNBC) cell line test • *In vitro* test on BT474 and MDA-MB-23 breast cell lines • *In vitro* test on HeLa cervical cancer cells	• Down-regulating miR-21 and inactivating PI3K/AKT/mTOR signaling pathway. • Downregulated the activations of RhoA and Rac1. • Apoptosis by cell cycle arrest. • Apoptosis by downregulating the PI3K/AKT and hTERT pathways.	• Zhu. *et al.*, 2021 • Lee *et al*., 2018 • Zhu *et.al,* 2019 • Kashafi *et al.*, 2017
• Luteolin	• Skin cancer • Prostate cancer • Ovarian cancer • Colon cancer	• *In vitro* test on JB6 P+ cell line and *in vivo* test on hairless mice model • *In vitro* PC-3 human prostate cancer cells test • *In vitro* cisplatin-resistant ovarian cancer (CAOV3/DDP) cells test and *in vivo* mice xenotransplant test • *In vitro* human colon cancer SW620 cells tets	• Inhibiting PKCε and Src kinase activity • Inhibiting ANO1 chloride channel • Apoptosis by downregulation of Bcl-2 expression in combination with cisplatin • Antitumor activity mediated by the ERK/FOXO3a signaling pathway	• Byun *et al.*, 2010 • Seo *et al.,* 2017 • Wang *et al.,* 2018 • Potočnjak *et al.,* 2020
• Chrysin	• Colon cancer • Breast cancer	• *In vitro* test on CT26 cells and *in vivo* mice xenotransplant test • *In vitro* MDA-MB-231cells test and *in vivo* xenograft mice test	• Apoptosis by increase in the caspase-3 and caspase-9 activity down regulation of the sall4 and up-regulation of the Bax • Inhibiting proliferation via PI3K / JNK and activating of GPER-mediated NF-κB signaling pathway	• Bahadori *et al*., 2016 • Kim *et al.,* 2020
Hesperetin	• Esophageal cancer •Glioblastoma • Gastric cancer • Lung cancer	• *In vitro* study on esophageal human cancer cells and *in vivo* study with xenografts on mice • *In vitro* tests on human GBM U-251 and U-87 cell glioma cells • *In vitro* test on human gastric cancer cell lines (HGC-27, SGC-7901, and MGC-803), and *in vivo* xenografts tumor model on nude mice • *In vitro* study *on* human lung adenocarcinoma A549 cells and *in vivo* test with xenograft model of lung cancer in nude mice	• Mitochondrial-mediated intrinsic pathway by accumulation of ROS • Oxidative damage in glioblasoma cells by increasing Bax/ Bcl-2 ratio • Inhibition of the PI3K/AKT signaling pathway and induce the mitochondrial pathway *via* upregulating PTEN expression • Decreasing the expression of P-gp and increased the intracellular accumulation of the P-gp substrate, rhodamine 123, in A549/DDP cells	• Wu *et al.*, 2016 • Li *et al*., 2020 • He *et al.*, 2020 • Kong *et al.*, 2020
Naringenin	• Breast cancer • Pprostate cancer • Lung cancer	• *In vitro* tests on human breast cancer cells (MDA-MR-231) and *in vivo* tests with an animal model with 7,12-dimethylbenz[a] anthracene (DMBA)-induced breast cancer in female rats • *In vitro* test on MDA-MB-231 breast cancer cells • *In vitro* study on prostate cancer cells PC3 and LNCaP • *In vitro* study on human lung cancer cells (A549)	• Inhibition of cell proliferation in association with with cell cycle arrest at the G0/G1 phase, and additionally promote apoptosis and deposition at the sub-G1 phase • Arresing the the cell cycle at the G2 phase and interfering with caspase-3 and caspase-9 activity • Promotion of apoptosis and ROS production, and decreasing the mitochondrial membrane potential, which led to increased Bax and decreased Bcl-2 proteins. Naringenin also reduced phosphorylation of ERK1/2, P53 P38 and JNK proteins • Reducing the expression of MMP-2 and MMP-9 and increase expression of caspase 3	• Zhao *et al.*, 2019 • Wang *et al.*, 2019 • Lim *et al.,* 2017 • Shi *et al.*, 2021
Jaceosidin	• Ssquamous cell carcinoma • Breast cancer • Cervical cancer	• *In vitro* test on oral squamous cell carcinoma (OSCC) cells (HSC-3 and Ca9.22) • *In vitro* test on MCF-7 breast cancer cells • *In vitro* test on cervical cancer cells, including SiHa and CaSki	• Accumulation of cells at the sub-G1 stage of the cell cycle and cleavage of caspase-9 and caspase-3 • Coaction between Bax and Bcl-2, striking a balance between cell survival/cell deaths • Inhibition of binding between oncoprotein E6 of the human papillomavirus and the p53 tumor suppressor protein	• Han *et al.*, 2018 • Ojulary *et al.*, 2020 • Lee *et al.*, 2005
Eupatilin	• Gastric cancer • Endometrial cancer • Glioma • Renal cancer	• *In vitro* test on human umbilical vein endothelial cells (HUVECs) and *in vivo* mouse xenografts test • *In vitro* test on human endometrial cancer cell lines Hec1A and KLE • *In vitro* test on human glioma cells • *In vitro* test on human renal cancer 786-O cells and *in vivo* test on nude mice	• Inhibiting the expression of signal transducer and activator of transcription 3, and the expression of vascular endothelial growth factor (VEGF) • Arresting the cell cycle at the G2/M phase through upregulation of p21 • Suppression of some transmembrane receptor expression, important for the proliferation and invasion of tumor cells (Notch-1) • Downregulating microRNA-21 through the activation of yes-associated-protein-1 (YAP1), which mediated the proapoptotic and antimigratory effects	• Cheong *et al.*, 2011 • Cho *et al.*, 2011 • Wang *et al.*, 2016 • Zhong *et al.*, 2019
Daidzein	• Bladder cancer • Breast cancer • Lung cancer	• *In vitro* bladder cancer cell lines and *in vivo* xenograft mice studies • *In vitro* tests on MCF-7 breast cancer cells • *In vitro* A 594 lung cancer cells	• G1 / S cell cycle arrest, down-regulation of the FGFR3 signaling pathway • Down-regulation of Bcl-2 and up-regulation of Bax, leading to the release of cytochrome C from mitochondria and on caspase-9 and caspase-7 activation • Reducing the levels of IL6 and IL-8, activation of p65-NFκB, Ki-67 and p65-NF-κB levels	• He *et al*., 2016 • Jin *et al.*, 2010 • Guo *et al.*, 2020

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Chapter 15
Flavonoids: A Functional Food With Anticancer Properties

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ABSTRACT

Flavonoids are biologically active phytochemicals that are naturally found in the everyday diet. They are bio-active polyphenolic compounds that have profound effects in inhibiting the growth and development of tumors. They are found to exert anti-tumor effects by acting in several ways: they modulate ROS production, regulate cancer cell proliferation, induce apoptosis, suppress the expression of pro-inflammatory cytokines with simultaneous increase in the expression of anti-inflammatory cytokines, and inhibit proto-oncogenes. Moreover, flavonoids eliminate the deleterious side effects of anti-cancer chemotherapeutic regimen. Thus, flavonoids can be used as a potential anti-cancer natural compound that not only achieves anti-cancer efficacy but also improves the survival and life expectancy of cancer patients.

INTRODUCTION

Flavonoids are a class of non-nutrient bioactive polyphenolic compounds that are found naturally in plants as a secondary metabolite. They are present in abundance as a constituent of different parts of flowering plants like bark, rhizomes, leaves, flowers and fruits of almost every plant. Although a large number of different flavonoid compounds are predicted to exist, there may be over 1000 flavonoid compounds in different plants, some of them exclusively found in dietary plants that are eaten daily and thus appears as an integral part of dietary foods (Pérez-Jiménez et. al., 2010). To date about 9000 flavonoids have been isolated from different plant sources (Xiao et. al., 2011). The flavonoids are synthesized from its precursor phenylalanine via the phenylpropanoid pathway in which phenylalanine is first converted into 4-coumaroyl-CoA with the help of phenylalanine ammonia lyase (PAL), which finally enters the flavonoid

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biosynthesis pathway in which 4-coumaroyl-CoA combines with 3-malonyl-CoA to form chalcones by the enzyme chalcone synthase. The basic structure formed in general phenylpropanoid pathway undergoes various modifications through enzymes to form different flavonoids in plants (Zhu et. al., 2015). There is no harm in this, although in recent times it has been suggested that dietary intake of natural flavonoids is able to protect humans from various diseases, such as infections and cancers (Swanson, 2015). It has been found to be protective against redox-mediated oxidative damage and in several degenerative diseases like cardiovascular diseases and other age-related diseases (Rice-Evans et. al., 1995; Kumar et. al., 2013; Khan et. al., 2021). Flavonoids as dietary supplements have also been found to protect the body from harmful side effects of therapeutic intervention carried out against many diseases, such as cancer and bacterial as well as viral infections. Thus it has been found to play an important role in the rehabilitation of chronic patients who have been undergone therapeutic treatment. However directional studies related to the role of flavonoids in different pathological conditions and in rehabilitation medicine as well is severely lacking; it has been considered that its major protective effects are due to its possession of anti-oxidant properties capable of acting in both *in vitro* and *in vivo* system (Rice-Evans et. al., 1995; Andreu et. al., 2017). Recently, it has been found that flavonoids are capable of showing an adaptogenic property on mice stress model (Habbu et. al., 2010) which is indicative of flavonoids being very effective in managing different pathophysiological conditions in different ways (Figure 1). Although it has already been established that it acts as a secondary antioxidant defense system in plant tissues exposed to various abiotic and biotic stresses (Kumar & Pandey, 2013) and thus naturally it is present in the nucleus as well as the location of mesophyll cells where generation of ROS takes place. Thus it appears to be a bioactive molecule that occurs naturally occurring in the natural system to protect it from the harmful insult of free radicals. However, detailed studies regarding the role of these dietary flavonoids in various pathophysiological conditions are severely lacking. Therefore, the present chapter is an attempt to discuss the role of dietary flavonoids in health and diseases and its future prospects in the management of various chronic health problems.

CLASSIFICATION OF FLAVONOIDS

The flavonoids are characterized by basic structure called flavan which is composed of two aromatic rings, ring A and ring B linked by a heterocyclic pyran ring, C (Figure 2). The structure is also known as benzo-γ-pyrone or phenylchromone and is a complex of 15-carbon phenylpropanoid chain having C6-C3-C6 carbon arrangement (Harborne, 1986; Harborne & Williams, 1992). The degree of oxidation in pyran ring, and hydroxylation and alkylation in benzene rings result in the formation of different types of flavonoid compounds that have slightly varied effects on the physiology. On the basis structural modification, the flavonoids can be classified into 6 major classes that are flavones, flavonones, flavanols, flavonols, isoflavonols, and anthocyanidins (Panche et. al., 2016; Durazzo et. al., 2019) (Figure 3).

Flavones

Flavones are characterized by the presence of unsaturated C ring at C2-C3 and ketonic group at C4 position where C3 is not occupied or hydroxylated. Benzene rings A and B are not hydroxylated at any carbon position. They are abundantly found in grains and herbs like celery, parsley, red peppers, chamomile, mint and *Ginkgo biloba* (Panche et al., 2016). The major flavones include apigenin, chrysin,

luteolin, tangeritin, etc. The flavone compounds found in the fruits and vegetables are known to contain a hydroxyl group at C5 position of ring A, while other hydroxyl groups at C7 position of ring A, C3 and C4 position of ring B may vary according to the class of vegetables. Polymethoxylated flavones, such as tangeritin, nobiletin and sinensetin are abundantly found in the zest or peels of citrus fruits, such as orange, lemon and grapes (Manach et. al., 2004).

Flavonone

They are an important class of flavonoids, also known as dihydroflavones which have oxidized C ring with ketone at C4 position of ring C like flavone and saturated C ring unlike to flavone. The flavonones are abundantly found in citrus juices, legumes, and tea and responsible for bitter taste of its juices and citrus peels. The main flavonones are hesperitin, naringenin and eriodictyol (Panche et. al., 2016; Kopustinskiene et. al., 2020).

Flavanol

Flavanols are also known as dihydroflavonols or catechins. They contain saturated C ring with hydroxyl group at C3 position of C ring unlike to flavonones. Since 3-hydroxy group of C ring is constantly present in the flavanol molecule, they are also referred to as flavan-3-ol. They are also known as tea catechins. The most predominent catechins are epicatechin which are found as stereoisomers, i.e., cis (-)-epicatechin or trans (+)-epicatechins according to C2-C3 position. They can form conjugate with gallic acid to form epicatechin gallate, epigallocatechin and epigallocatechin gallate (Babu & Liu, 2008; Rosen, 2012; Braicu et. al., 2013). They are abundantly found in tea, bananas, apples, blueberries, peaches and pears (Table 1).

Flavonol

Flavonol are similar to flavone in the backbone, except for a hydroxyl group at the C3 position of ring C. They have unsaturated C ring at C2-C3 and a ketone group at C4 position. They may be found as glycosylated forms. They are regarded as building blocks of proanthocyanins and are abundantly found in oninons, kale, lettuce, tomatoes, apples, grapes and berries. They are also found in high amount in tea and red wine (Panche et al., 2016). The major flavonols are kaempferol, quercetin, myricetin and fisetin which are also most studies flavonoids.

Anthocyanidin

Anthocyanidins are unsaturated flavonoids with basic structure of the 2-phenyl-benzopyrylium chromophore-flavylium ion. They are unsaturated at C1-C2 and C3-C4 carbon position of ring C. They are hydroxylated at C3 position of ring B and in some of anthocyanidin molecules, hydroxylation may occur at C3, C4 and C5 position in the ring B (Abotaleb et. al., 2018). They are basically pigments found predominantly in the outer layers of many fruits, such as cranberries, black currants, red grapes, raspberries, strawberries, blueberries, blackberries, etc., and responsible for their vibrant colors of their flowers and fruits. However, the color of anthocyanidins is largely dependent on the pH balance which can be affected by methylation and acylation at the hydroxyl groups on ring A and ring B (Iwashina,

Table 1. Overview of flavonoids and their natural sources

Flavonoid subclass	Flavonoid compounds	Natural sources
Flavones	Apigenin, Baicalein, Chrysin, Diosmetin, Luteolin, Rhoifolin, Rutin, Tangeratin, Tricin	Fruits, fruit skins, tomato skins, red wine, red pepper (*Capsicum annuum*), buckwheat (*Fagopyrum esculentum*) and some medicinal plants and others such as *Aloe vera* (Luteolin), *Bacopa moneirra* (Luteolin), *Mentha longifolia* (Luteolin-7-O-glycoside), *Momordica charantia* (Luteolin), *Oroxylum indicum* (Chrysin)
Flavonone	Abyssinones, Eriodictyol, Hesperitin, Hesperidin, Naringin, Naringenin, Taxifolin	Citrus fruits such as oranges, lemons, grapefruits, *Citrus medica* (hesperidin), and some medicinal plants
Flavanol	(+)-Catechins, (-)-Epicatechin, Epigallocatechin, Epicatechin gallate, Epigallocatechin gallate, Theaflavin	Tea (*Camellia sinensis*), Bananas (*Musa paradisiaca*), Apples (*Malus domestica*), Blueberries (*Cyanococcus*), Peaches (*Prunus persica*) and Pears (*Pyrus sps*)
Flavonol	Fisetin, Kaempferol, Myricetin, Quercetin, Tamarixetin	Vegetables such as onion (*Allium cepa*), fruits such as berries and grapefruit (*Citrus paradisi*), red wine, olive oil (*Olea europaea*) and some medicinal plants such as Indian copperleaf (*Acalypha indica* – Kaempferol glycosides), Aparajita (*Clitoria ternatea* - Kaempferol-3-neohesperidoside), Neem (*Azadirachta indica* – Quercetin), Common silver birch (*Betula pendula* – Quercetrin), Hemp (*Cannabis sativa* – Quercetin)
Anthocyanidin	Apigenidin, Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Fruits such as cherry (*Prunus avium*), black currants (*Ribes nigrum*), red grapes (*Vitis vinifera*), blue berries (*Cyanococcus*), blackberries (*Rubus fruticosus*), raspberry (*Rubus idaeus*) and strawberry (*Fragaria ananassa*), vegetables such as bell peppers (*Capsicum annuum*), etc., some nuts and dried fruits
Isoflavonone	Biochanin, Daidzein, Daidzin, Genistin, Genistein, Glycitein	Soyabeans (*Glycine max*) and some other legumes such as chick pea (*Cicer arietinum*), lupin seeds (*Lupinus sps*), etc., and some medicinal plants such as flame of the forest (*Butea monospermea* – Genistein),
Chalcones	Arbutin, Chalconaringenin, Phloridzin, Phloretin	Tomatoes (*Solanum lycopersicum*), pears (*Pyrus sps*), strawberries (*Fragaria ananassa*), bearberries (*Arctostaphylos uva-ursi*) and certain wheat varieties

Sources: (Kumar & Pandey, 2013; Panche et. al., 2016)

2013). Due to their vibrant color derived from organic sources, they are often used in the food industry. Major anthocyanidin molecules are cyanidin, delphinidin, malvidin, pelargonidin, petunidin, and peonidin (Abotaleb et. al., 2018).

Isoflavonone

Isoflavonoids are characterized by a chromane ring attached to a ring B at C3 position on ring C unlike to C2 position as in other flavonoids (Panche et. al., 2016). Isoflavonoids have a very limited distribution in plants, although they have been found to play an important role in the formation of phytoalexins (isoflavonoid phytoalexin) during invasion of microbes in plants (Aoki et. al., 2000; Dixon & Ferreira, 2002). They are predominantly found in soyabeans and other legumes. In 2008, Matthies et. al. reported that isoflavonoids are also found in some microbes residing in the mouse intestine. The major isoflavonoids are genistin, genistein, daidzin, daidzein, glycitein, etc. Genistein and daidzein are commonly regarded as phyto-estrogens due to its oestrogenic activity in certain animal models where they are capable of inducing hormonal and metabolic changes (Szkudelka & Nogowski, 2007).

Chalcones

Chalcones are distinct class of flavonoids which are characterized by the absence of ring C in basic flavan structure. Therefore, it is also referred to as open-chain flavonoids. The main examples of chalcones are arbutin, chalconaringenin, phloridzin and phloretin. They are predominantly found in tomatoes, pears, strawberries, barberries and certain wheats varieties. They are comparatively less studied flavonoids but they are known to contain multitude of pharmacological properties including antiviral and anticancer (Marinov et. al., 2020; Salehi et. al., 2021).

METABOLISM OF FLAVONOID

As discussed, the flavonoids are richly and ubiquitously distributed in various plants that are part of our diet including fruits, vegetables, legumes, nuts, and derived beverages, such as tea, wine and fruit juices with different concentration (Pérez-Jiménez et. al., 2010). Since these plant products are part of daily diet throughout the globe, the flavonoids are taken habitually by the people. However the amount of flavonoids intake vary according to the food habit. It has been estimated that the mean intake of flavonoids ranges from 150 to 600 mg/day (expressed as aglycones only) worldwide (Johannot & Somerset, 2006; Chun et. al., 2007; Zamora-Ros et. al., 2012; Zhang et. al., 2014; Jun et al., 2015; Zamora-Ros et al., 2018). The lowest daily intake of flavonoids is in Brazil and the highest value is in Australia, thus it can be said that the daily intake of flavonoids ranges from 11 mg/day to 629 mg/day. Asians are known to have a higher intake of dietary flavonoids than American and European populations, although the daily intake value in these countries, in particular UK under study, vary and is largely dependent on daily intake of tea (Kent et. al., 2015; Miranda et. al., 2016). Further, its intake varies locally as for example in Europe, an increasing south-to-north gradient is generally observed. It has been found that total flavonoid intake in Mediterranean (MED) countries (250-400 mg/ml) is lower than in non-MED countries (350-600 mg/day) despite the high intake of fruits, vegetables, and red wine in Mediterranean (MED) countries, even without taking into account thearubigins.

After dietary intake of flavonoids, they go directly into the alimentary canal for absorption which is highly dependent on its physicochemical properties, such as molecular size, complexity, configuration, lipophilicity, solubility, and pKa. Most flavonoids, except catechins, are present as a complex structure and bound to sugars as flavonoid β-glycosides. The glycosidation of flavonoids results in broadly two classes of flavonoids, i.e., flavonoids glycosides and aglycone falvonoids (Figure 4). Flavonoids glycosides take longer to be assimilated than aglycones. Aglycones seem to be easily absorbed and its absorption starts in small intestine, while flavonoid glycosides need to be converted into aglycone by glycoside hydrolases or β-glycosidases or Lactase-phlorizin hydrolase (LPH) in association with intestinal microflora before their absorption as a first step (Day et. al., 1998). Some flavonoid glycosides that are still unhydrolyzed are absorbed through the sodium glucose transporter 1 (SGT1) in large intestine (Chen et. al., 2014). Approximately only 10% of the flavonoid glycosides undergo absorption in intestine while most of the absorption is accomplished in colon (Hervert-Hernández & Goñi, 2011). Only glucoside forms are absorbed through small intestine (Hollman, 2004). After absorption, they are conjugated with glucuronide or sulfate to form glucoronide flavonoid or flavonoid sulfate or modified into its methylated form by phase II enzymes, such as sulfotransferase (SULT), uridine-5′-diphosphate (UGT) and others through the process of glucuronidation, sulfation and methylation in epithelial cells and liver. The intestinal micro-

biota plays an important role in their absorption through the process of deglycosylation and catabolism, such as reduction and ring cleavage. After absorption, they enter liver where they are modified by oxidation, reduction, decarboxylation, demethylation, isomerization before entering to systemic circulation (Murota et. al., 2018). Thus, the flavonoid in blood constitutes glycosylated flavonoid, caroboxylated flavonoid, methylated flavonoid and sulfated flavonoid that induces flavonoid-led biological activity in human (Murota et. al., 2018). Therefore, none of the flavonoids are found as aglycone in the circulation (Figure 5). From the systemic circulation, they are either excreted through the urine or secreted in the bile which is later broken down by intestinal bacteria in colon (Hollman, 2004).

ANTICANCER PROPERTIES OF FLAVONOID

Flavonoids are considered as health promoting bioactive compound that have protective role in disease prevention in various disease conditions like cardiovascular disease, diabetes, neurodegenerative disorder, infection, etc., and reduces mortality of individual (Rahman & Mondal, 2020). They have been reported to act as a hepatoprotective, an antioxidant, antithrombotic, anti-allergic, anti-inflammatory, anti-bacterial and anti-cancer agent thereby they are beneficial in promoting life condition of patients suffering from chronic disease especially in cardiovascular diseases and cancer (Anand Babu & Liu, 2009).

Cancer is a heterogeneous disease characterized by uncontrolled growth of abnormal cells in response to impairment in regulatory mechanism of cell division and mutation in tumor suppressor genes or activation of proto-oncogene (Velez & Howard, 2015). The transformed or abnormal cells failed to undergo programmed cell death or apoptosis and therefore they continued to grow as a population of abnormal cells and metastasize to other parts of the body. The transformation of cells and tumor development is mainly due to impairment of DNA repair mechanism, oxidative stress, prolonged or chronic inflammation, infection, pollution, smoking, exposure of chemical carcinogen, stress, radiation and ultraviolet light (Lotze, 2004; Blackadar, 2016; Srihari, 2017; Kao, 2018; Neagu et. al., 2019). Cancer is also associated with mitochondrial dysfunction that leads to deregulated energy supply, increased reactive oxygen species (ROS) generation, compromised metabolic function reflected by increased production of lactate dehydrogenase (LDH) which are typical of tumor tissues (Kroemer & Pouyssegur, 2008; Neagu et. al., 2019; Bock et. al., 2019). Elevated level of LDH causes tumor microenvironment to be more acidic which further favors inflammation and thus tumor development, growth and metastasis (Lee & Kim, 2016). Flavonoids are demonstrated to exert anti-cancer effects in many ways. The anticancer effect of flavonoid emphasizes the role of dietary factors to be important in managing tumor growth and development. In this line, seasonal fruits and fresh vegetables have been recommended as dietary supplement for chemoprevention of cancer (Ho et. al., 1994; Mishra et. al., 2013). It has been evidenced that inclusion of more fruits and vegetables or use of flavonoids as nutraceuticals reduced the possibility of developing cancer (Le Marchand, 2002; Chun et. al., 2005). Consumption of onions alone or together with apples that are major source of flavonol quercetin, have been shown to diminish incidence of prostate cancer, lung cancer, stomach cancer, and breast cancer. Moreover, consumption of moderate amount of wine have been found to be associated with lower risk of developing lung cancer, ovarian cancer, esophageal cancer, stomach cancer and colon cancer (Brusselmans et. al., 2005). These relationships of dietary flavonoids in reducing risk of cancer and their use in cancer prevention have been extensively studied. The potential of flavonoid as anti-cancer agents gained much emphasis after the preliminary work of Dai et. al., 2002, who demonstrated in his case-control type study on 250 breast

cancer patients in Shanghai that a significant number of breast cancer patients had less isoflavonoid and lignans in their urine collected prior to chemotherapy compared to the control group. A series of case-control studies had since been conducted to understand the relationship of dietary flavonoids in reducing cancer risk and for use in cancer prevention, such as impact of quercetin consumption in lung cancer in Finnish population (Knekt et. al., 2002), onions, white grapefruits, apples and quercetin in lung cancer in Hawaiian population (Le Marchand et. al., 2000), catechins in oesophageal and epithelial cancer in Zutphen population (Arts et. al., 2001) and postmenopausal cancer in women between ages of 55 and 69 in Iowa elderly women population (Arts et. al., 2002; Cutler et. al., 2008), and so on.

Flavonoids exert anti-cancer effects by influencing a various biochemical processes, such as scavenging of ROS, regulation of cell cycle, suppression of cell proliferation, enhancing genome stability, apoptosis, induction of autophagy, and other immunomodulatory as well as anti-inflammatory processes (Gorlach et. al., 2015; George et. al., 2015; Yahfoufi et. al., 2018; Abotaleb et. al., 2018; Chirumbolo et. al., 2018; Perez-Vizcaino & Fraga, 2018; Rodríguez-García et. al., 2019). They also activate other chemopreventive processes capable of inhibiting/suppressing tumor growth and progression (Liao et. al., 2015; Amawi et al., 2017).

Flavonoids in Oxidative Stress

Oxidative stress is a physiological condition caused by an imbalance between production and accumulation of free radicals or reactive oxygen species (ROS) and anti-oxidants in the cells leading to cell and tissue damage (Pizzino et. al., 2017). Normally they are produced as by-products of energy metabolism in mitochondria in response to environmental stressors like ultraviolet (UV) radiation, ionizing radiations, and exposure of pollutants and heavy metals (Murphy, 2008). Xenobiotic compounds, such as plants constituents, drugs, pesticides, cosmetics, flavorings, fragrances, food additives, industrial chemicals, etc., and antiblastic drugs, such as antineoplastic agents, interferons, cytarabine, interferon gamma receptor, platelet-derived growth factor receptor, tumor necrosis factor (TNF)-α receptor, etoposide, cisplatin, daunorubicin, etc. also contribute in the production of ROS. Although ROS is not harmful at optimal levels and plays an important role in cell signaling, its high concentration results in the development of inflammation that contributes to tumor growth and progression (Liou & Storz, 2010; Aggarwal et. al., 2019). Flavonoids have been shown to exert both anti-oxidant as well as pro-oxidant effect in the cells; with this respect on one hand they scavenge free radicals or ROS and on the other hand as a potent pro-oxidant, they activate apoptosis, necrosis and autophagy (Hadi et. al., 2000; Link et. al., 2010). They have also been reported to directly scavenge the ROS and increases metal chelation of ROS (Youn et. al., 2006). It has been later suggested that it enhances metal chelation due to the presence of phenolic hydroxyl groups which are able to stabilize free radicals (Fraga et. al., 2010). Indirectly flavonoids reduces the level of free radicals by activating antioxidant enzymes, such as catalase, glutathione peroxidase (GPX) and peroxiredoxins (Prx), while inhibit pro-oxidant enzymes, such as SOD, NOX and xanthine oxidase (XOD) (Figure 6). Both anti-oxidant and pro-oxidant properties of flavonoids are known to contribute to anticancer effects (Valko et. al., 2007; Oliveira-Marques et. al., 2009).

Flavonoids in Apoptosis

Besides the role of ROS-mediated apoptosis in tumor cells, flavonoids are capable of activating canonical apoptotic pathway. Immortality is a characteristic of tumor cells; it is therefore a prerequisite to rein-

Table 2. Effects of flavonoids on ROS and ROS-mediated suppression/inhibition of growth and progression of tumors

Flavonoid	Subclass of flavonoids	Anti-tumor property	Reference
Genistin	Isoflavone	Induces ROS-dependent apoptosis	Kaushik et. al., 2019
Daidzein	Isoflavone	Induces ROS-dependent apoptosis in MCF-7 breast cancer cells	Jin et. al., 2010
Hesperetin	Flavonone	Induces mitochondrial apoptotic pathways by increasing the generation of ROS in gall bladder carcinoma, esophageal carcinoma, hepatocellular carcinoma, and human breast cancer cell line MCF-7 cells	Pandey et. al., 2018; Wu et. al., 2015; Zhang et. al., 2015; Palit et. al., 2015
Naringenin	Flavonone	Induces mitochondrial apoptotic pathways by increasing the generation of ROS and activating signaling pathways in choriocarcinoma JAR and JEG cell lines, human epidermoid carcinoma A431 cell line, and PC3 and LNCaP prostate cancer cell lines.	Park et. al., 2018; Ahamad et. al., 2014; Lim et. al., 2017
Catechins	Flavanol	Induces morphological changes, DNA damage and apoptosis in epithelial ovarian cancer cells by increasing the generation of ROS, and activates glutathione peroxidase and reductase by activating ERK1/2 pathway in HepG2 cell lines	Martin et. al., 2010
Procyanidins	Anthocyanidin	Induces morphological changes, DNA damage and apoptosis in epithelial ovarian cancer cells by increasing the generation of ROS, and protects Caco2 human colorectal adenocarcinoma cells reducing oxidative stress	Taparia & Khanna, 2016; Rodríguez-Ramiro et. al., 2010; Martín et. al., 2016
Cyanidin	Anthocyanidin	Induces apoptosis in metastatic cancer cell lines LoVo and LoVo/ADR by increasing ROS generation and glutathione reductase suppression	Cvorovic et. al., 2010
Delphinidin	Anthocyanidin	It also Induces apoptosis in metastatic cancer cell lines LoVo and LoVo/ADR by increasing ROS generation and glutathione reductase suppression	Cvorovic et. al., 2010
Quercetin	Flavonol	Reduces the proliferation of hepatocellular carcinoma HepG2 cells by decreasing ROS generation; however induces apoptosis in human gastruic cancer cell line AGS and human breast cancer cell line MCF-7 cell line by increasing ROS generation	Shang et. al., 2018; Wu et. al., 2018; Jeon et. al., 2019
Kaempferol	Flavonol	Suppresses the growth of cancerous bladder cells by ROS-mediated apoptosis and cell cycle arrest in S phase, induces caspase-mediated apoptosis in colorectal cancer HCT116, HCT15 and SW480 cell lines, and induces mitochondrial apoptotic pathways in rat hepatocellular carcinoma cells	Wu et. al., 2018; Choi et. al., 2018; Seydi et. al., 2018
Apigenin	Flavones	Induces ROS-mediated apoptosis in ovarian cancer cell lines A2780, OVCAR-3 and SKOV-3, and induces mitochondrial apoptotic pathways by increasing the production of ROS in human cervical cancer-derived cell lines, such as HeLa, SiHa, CaSki and C33A cell lines	Tavsan & Kayali, 2019; Salmani et. al., 2017; Souza et. al., 2017
Luteolin	Flavones	Induces ROS-mediated apoptosis in ovarian cancer cell lines A2780, OVCAR-3 and SKOV-3	Seydi et. al., 2018; Tavsan & Kayali, 2019
Chrysin	Flavones	Induces apoptosis by enhancing the production of ROS and peroxidation level in choriocarcinoma cell lines JAR and JEG3, bladder cancer, and ovarian cancer cell line ES2 and OV90	Lim et. al., 2017; Park et. al., 2018; Xu et. al., 2018

state the mortality of tumor cells by inducing apoptosis. Therefore it is inevitable to modulate apoptotic pathway through the use of dietary flavonoids (Yan et. al., 2017).

Apoptosis is executed by the activation of two types of signal cascades, that is, extrinsic and intrinsic signal cascades. Extrinsic pathways involves signaling from extrinsic factors like tumor necrosis factor (TNF) superfamily proteins leading to the activation of caspase 9, 3 and 7 (Fan et. al., 2005; Abotaleb et. al., 2018; McArthur & Kile, 2018), while intrinsic pathway of apoptosis is activated from signals within the cells (Fulda & Debatin, 2006). Flavonoids, such as apigenin, luteolin, baicalein and chrysin reported to exhibit inhibitory effect on proteasome system (Koosha et. al., 2016; Moga et. al., 2016; Yan et. al., 2017; Amawi et. al., 2017). Flavonoids target apoptotic signaling cascade by regulating expression proto-oncogenes like *cMyc* leading to the regulation of expression of Bcl-2 family proteins and increased expression of p53 proteins (Jan & Chaudhry, 2019). Further, they act as pro-oxidants and inhibit epidermal growth factor receptor/mitogen activated protein kinase (EGFR/MAPK), phosphatidylinositide 3-kinases (PI3K) (Figure 7), protein kinase B, nuclear factor – kappa B (NF-κB) leading to suppression in proliferation of cancer cells (Rodriguez-Garcia et. al., 2019; Neagu et. al., 2019; Abotaleb et. al., 2018). The study on the effect of different flavonoids in activating apoptosis has been studied widely in different tumor models, such as A2780, HCT-116, LoVo, MCF-7, HCCK-HEP-1, MDA-MB-231, PC-3 cell lines (Shafiee et. al., 2016; Liu et. al., 2012; Zhang et. al., 2015; Sambantham et. al., 2013). Naringenin, a flavonone, is known to decrease the expression of survivin and Bcl2, in addition to increased expression of p53 to induce extrinsic apoptotic cascade as evident from study on SGC-7901 cell line (104, 105), whereas hesperetin flavonone has been demonstrated to induce the release of cytochrome C which leads to the activation of caspase 3 and caspase 9, and reduces Bax to Bcl-2 ratio in gastric carcinoma, Eca109 cell line, HT-29, MCF-7, and MDA-MB-231 cell lines (Zhang et. al., 2015; Wu et. al., 2015; Palit et. al., 2015; Sivagami et. al., 2012). Other flavonoids, such as daidzein, catechins, etc., follow comparable pathway to achieve anti-cancer effect by inducing apoptosis in various cancer cell lines (Kopustinskiene et. al., 2020).

Anti-Proliferative Property

Flavonoids are considered to be a potential anti-proliferative agent. Anti-proliferative property allows flavonoids to check/suppress and/or inhibit the progression and spread of tumor cells in the body. There are at least 27 flavonoid compounds, mostly form citrus fruits sources that have been investigated for their anti-proliferative property (Kandaswami et. al., 1991). Citrus fruits are rich in multitude of flavonoid compounds including flavonoid glycosides, polymethoxylated flavones, etc. Most of the flavonoids studied have shown promising anti-proliferative effect (Manthey et. al., 2001). However 7 flavonoid compounds from citrus fruits were found to be very active against several tumor cell lines in checking the growth and progression; other compounds from citrus fruit preparation have been found to be weak in limiting the growth of tumor cells as evidenced form their effect on normal human cell line (Kawaii et. al., 1999). These flavonoid compounds are luteolin, quercetin, tangeretin, eriodictyol, nobiletin, and 3,3',4',5,6,7,8-heptamethoxyflavone. Luteolin has been judged to be most effective anti-proliferative agent out of these 7 compounds, then there is quercetin in terms of degree of efficacy and 3,3',4',5,6,7,8-heptamethoxyflavone has lowest anti-proliferative property (Kawaii et. al., 1999). Polymethoxylated flavones have been shown to be more potent anti-proliferative compound than the flavonoid glycoside. Other hydroxylated flavone and aglycone showed strong anti-proliferative effect as well. Further, it has been found that flavones induce stronger anti-proliferative affect compared to flavonone (Manthey & Guthrie, 2002). Therefore, it has been suggested that glycosylation of flavonoid compounds probably eliminates the anti-proliferative property of flavonoids. Thus, it can be assumed that only those flavonoids which do

not have glycosidic linkage are potent anti-proliferative agents. Further, the structure-activity relationships of different flavones and flavonones have been carried out in different tumor models by Ramanouskaya et. al. in 2009 and found that the ortho-catechol moiety in ring B and a C2-C3 unsaturation are important for the anti-proliferative function of flavonoids.

The anti-proliferative effect of flavonoids has been achieved through multiple mechanisms; however not all flavonoids share anti-proliferative effect (Forni et. al., 2008). The flavonoid compound exert regulatory effect on the cell cycle by docking in the ATP binding pocket of phosphoinositide 3-kinase gamma (PI3Kγ) and cause cell cycle arrest at G2/M phase (Zhang et. a., 2018). They down-regulate the expression of PI3K γ-p110, phosphor-PI3K, Phospho-AKT, phosphor-mTOR, phosphor-p70S6K and phosphor-ULK in response to flavonoids leading to cell cycle arrest and induction of apoptosis and autophagy in several tumor models (Figure 7) which are under study reflecting the importance of flavonoids in cancer treatment (Li et. al., 2014; Chen et. al., 2017; Embrahimi et. al., 2017; Raffa et. al., 2017). Synthetic inhibitor of PI3Kγ like AS605240 potentiates flavonoids and showed additive effects in mediating inactivation of AKT kinase such as serine/threonine kinase, mammalian target of rapamycin (mTOR), p70S6K, ULK (Unc-51 like autophagy activating kinase) and apoptosis (Zhang et. al., 2018). Inhibition of cell cycle regulatory enzymes and resultant inhibition of cell proliferation, inhibition of vascular endothelial growth factor (VEGF) via inhibition of matrix metalloproteinases (MMP) inhibit angiogenesis which further limits the spread and metastasis of tumor cells in the host (Fotsis et. al., 1997; Kim, 2003; Mirossay et. al., 2017).

Flavonoids and Tumor Cell Cytotoxicity

Flavonoids are not cytotoxic to optimal level but high level of flavonoids has been demonstrated to exert cytotoxic effect to tumor cells (Lu et. al., 2005; Morales & Haza, 2011; Rao et. al., 2011). Since dietary composition of flavonoids is highly variable, it is difficult to take the required level of flavonoids through dietary intake (Ou et. al., 2013; Rao et. al., 2011). The required dose of flavonoids for cytotoxic effect is in the milligram range, which needs consumption of a large volume of flavonoid containing diet, for example, intake of a full glass of orange juice gives only 0.5 μM of plasma concentration of naringenin (Jin et. al., 2009) and 0.5 – 0.6 μM of hesperetin (Yang et. al., 2012), 550 g of grapefruit juices attains only 6 μM of mean plasma concentration of naringenin (Harmon & Patel, 2004), and so forth. Therefore, to achieve cytotoxicity in tumor cells, they need to be taken in purified forms. Cytotoxicity of different flavonoids has shown to be varied and depending upon sensitivity of tumor cells towards flavonoids (Himeji et. al., 2006; Kilani-Jaziri et. al., 2011). The cytotoxicity effect of flavonoids has been achieved through implying various mechanisms of cell death such as caspase-dependent apoptosis, mitochondria-dependent apoptosis, and anti-proliferative effect (Molčanová et. al., 2019).

Anti-inflammatory Properties of Flavonoids

Inflammation is a characteristic feature of most of the tumors. Chronic inflammation causes tumor development by inducing cell transformation due to log-term exposure of normal cells in inflammatory microenvironment which is said to be pro-tumor physiochemical process (Gupta et. al., 2018). Chronic inflammation also leads to tumor cell invasion, metastasis through escalated growth, degradation of matrices due to increased expression of matrix metalloproteinases (MMP) and induction of angiogenesis in tumor tissue (Coussens & Werb, 2002; Grivennikov et.al., 2010; Landskron et. al., 2014). They

are known to exert immunomodulatory action by activating several immune cells which in turn release anti-inflammatory cytokines by activating transcription factors nuclear factor-kappa B (NFκB) (Choy et. al., 2019). They are demonstrated to reduce T cell differentiation to T helper and T cytotoxic cells and induce the differentiation of T regulatory cells by inhibiting the activity of mTOR (Hosseinzade et. al., 2019). Moreover, they are known to be a potent suppressor of programmed cell death ligand-1 (PD-L1) expression which are important for generation of pro-inflammatory microenvironment (Bao et. al., 2019). They can suppress other molecules also which are involved in the generation of pro-tumor microenvironment, such as AKT, ERK, MAPK, COX-2, iNOS, and related biomolecules (Figure 9).

In this line, quercetin have been shown to exert anti-inflammatory effects in the case of coronary artery disease (CAD) where chronic systemic inflammation (CSI) is a characteristic feature, by decreasing pro-inflammatory cytokines levels in blood serum, such as IL-1β and TNF-α through the down-regulation of NF-κB in blood mononuclear cells (Nair et. al., 2006; Chekalina et. al., 2018), in leptin-induced inflammation model using human umbilical vein endothelial cells (HUVECs) (Indra et. al., 2013), and in a neonatal rat cardiac fibroblast cells (Tang et. al., 2014). Further quercetin has been found to inhibit the expression of matrix metalloproteinases MMP9 and MMP 2 in human glioblastoma U251 tumor cell line (Liu et. al., 2017). Luteolin has been found to increase the production of nitric oxide (NO), reduce the expression of NF-κB thereby reducing the expression of pro-inflammatory cytokines, such as TNF-α. Luteolin also inhibits the degradation of inhibitor of nuclear factor kappa B (IκB)-β and nuclear translocation of NF-κB, and reduces the NF-κB DNA binding to achieve anti-inflammatory microenvironment (Lv et. al., 2010; Oyagbemi et. al., 2018). Fisetin has been known to attenuate the expression of NF-κB thereby reducing the expression of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in blood serum of cardiac myopathy of diabetic rats (Althunibat et. al., 2019; Garg et. al., 2019). Apigenin inhibits the expression of pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α produced in response to LPS-mediated activation of macrophages by the down-regulated activity of MAPK and NF-κB (Kim & Joo, 2011; Izzi, 2012). Apigenin is also known to inhibit the expression of PD-L1 on the surface of A375 melanoma cells which lead to reduced expression of pro-inflammatory cytokines (Bao et. al., 2019). Likewise flavonone hesperetin suppresses the secretion of TNF-α, IL-6 and IL-1β, decreases the production of NO by decreasing inducible nitric oxide synthase (iNOS) and COX-2 gene expression, and down-regulating NF-κB activation by suppressing NF-κB phosphorylation in LPS-induced RAW264.7 cells (Ren et. al., 2016).

All these studies suggest that flavonoids are capable of exerting anti-inflammatory effect and reducing the pro-inflammatory microenvironment formation in various tumor cells, thus capable of suppressing the growth and progression of tumor by suppressing the formation of pro-tumor microenvironment.

Effect of Flavonoids in Cell Mediated Immunity

Cell mediated immunity is achieved by the action of T helper cells ($CD4^+$ T cells) and cytotoxic T cells ($CD8^+$ T cells). $CD4^+$ T cells secrete cytokines that act as mediator of immune response by potentiating the function of other immune cell types, such as macrophages and B cells (Araki et. al., 2011; Odegaard & Chawla, 2013). $CD4^+$ T cells are of two types, viz. T helper 1 (Th1) and T helper 1 (Th2) cells. Cytokines secreted by Th1 cells are known as Th1 cytokines that are important for the generation of cell-mediated immunity and Th2 cells secrete Th2 cytokines which antagonize the cell-mediated immune responses. The profile of cytokines secreted by these cells directs the type of antibodies produced by B cells and polarization of monocytes and macrophages at the microenvironment (Zhu et. al., 2010). Martinez et. al.

in 2019 reported that a number of flavonoids, such as apigenin, quercetin and Epigallocatechin-3-Gallate (EGCG) inhibit various transcription factors that modulate the differentiation, proliferation and activation of various immune cells by exerting anti-inflammatory effects through NF-κB inhibition thereby inhibiting the production of IL-1β, IL-2, IL-6, TNF-α, IL-17A, chemokines and RNI and ROS. These biomolecules have the potential to activate Th2 cell population to secrete Th2 cytokines that suppresses the cell-mediated immunity, while inducing the development of humoral immunity. Evidences on direct effect of flavonoids on helper T cells and cytotoxic T cells are severally lacking. However, it is clear that flavonoids are able to suppress Th1-specific immune response while activating Th2-specific immune response (Martinez et. al., 2019).

FLAVONOIDS IN CANCER TREATMENT

Considering the role of flavonoids in elevating anti-tumor microenvironment, the flavonoids have been studied for their use in anti-cancer treatment strategy. In its first preliminary study, Kawaii et. al. in 1999 studied the effect of some flavonoids sourced from citrus fruits on the rat oral cancer model chemically induced by the use of 4-nitroquinoline 1-oxide and found that the citrus flavonoids are able to inhibit the proliferation of cancer cells, such as lung carcinoma cells A549 and gastric TGBC11TKB cancer cell lines. The clinical studies related to the use of different potent flavonoids in human cancer models are severely lacking, however it has demonstrated that flavonoids have not shown any negative effect on human normal cells (Sak, 2014). Soyabean isoflavones administration to prostate cancer patients in several clinical studies showed that the soyabean isoflavone administration enhances prostate-specific antigen levels (Messina et. al., 2006), which indicates that isoflavone administration results in the activation of several immune cell population in these cancer patients. In a similar kind of study in European men, it has been reported that higher level of blood serum level of genistein are associated with a lower risk of prostate cancer (Travis et. al., 2009).

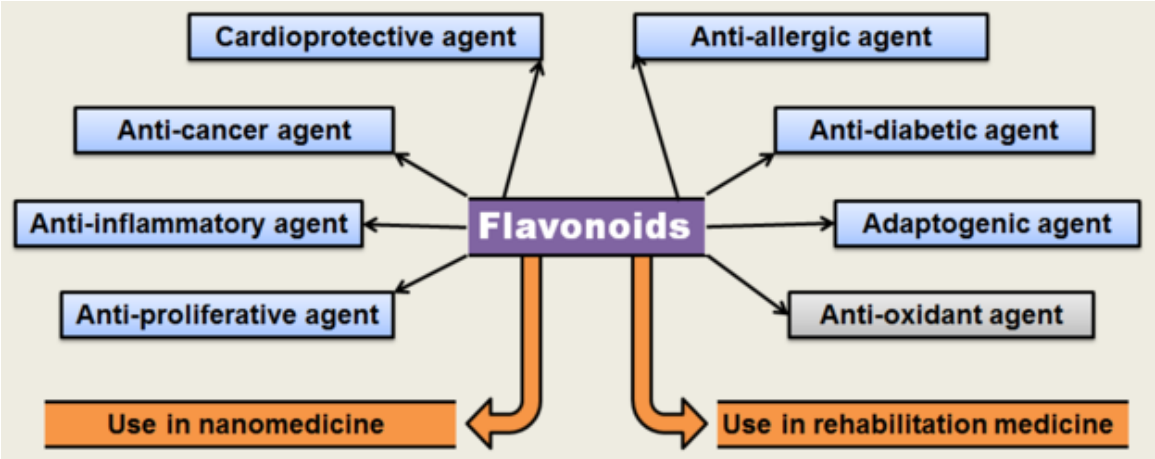
CONCLUSION

Flavonoids are the potential biomolecules derived from natural sources that can play beneficial role in limiting the growth and progression of cancer. Cancer is a multifactorial and heterogeneous disease characterized by uncontrolled cell division and resistance to apoptosis being the most important. Cancer stands top among most fatal disease of mankind. The only approach for the treatment of cancer, today, is chemotherapeutic approaches that fill hope in the cancer patient and the chemoprevention is working well in preventing occurrence and death of the cancer patients. However the chemotherapeutic regimen has several side effects that compromise the life expectancy of cancer patients. Flavonoids have no side effects but able to suppress/repress the development, growth and progression of tumor cells through various anti-cancer processes (Zheng et. al., 2002; Anter et. al., 2011) and therefore combining flavonoids with present chemopreventive regimen can not only help in curing of cancer patients but also help in enhancing survival life of the cancer patients. Anti-cancer property of flavonoids indicates that diet can be combined with different health condition to make a health-diet combination for better and effective health management with no or least side effects. The use of dietary flavonoids can ensure the greater

chemoprevention compared to administration of single chemotherapeutic agent alone (Iwuchukwu et. al., 2011).

FIGURE LEGEND

Figure 1. Overview of role of flavonoids in health and diseases



Flavonoids play a multidimensional role in health and diseases of an individual. It protects the individual from various internal and external stressors and strengthens cardiovascular system. It acts as anti-proliferative and anti-inflammatory agents and thus also plays an important role in limiting the growth and progression of cancer. Due to its broad role in health and diseases, it is often used in rehabilitation therapy in critical illness and, in addition, studies are underway for its use in nanomedicine.

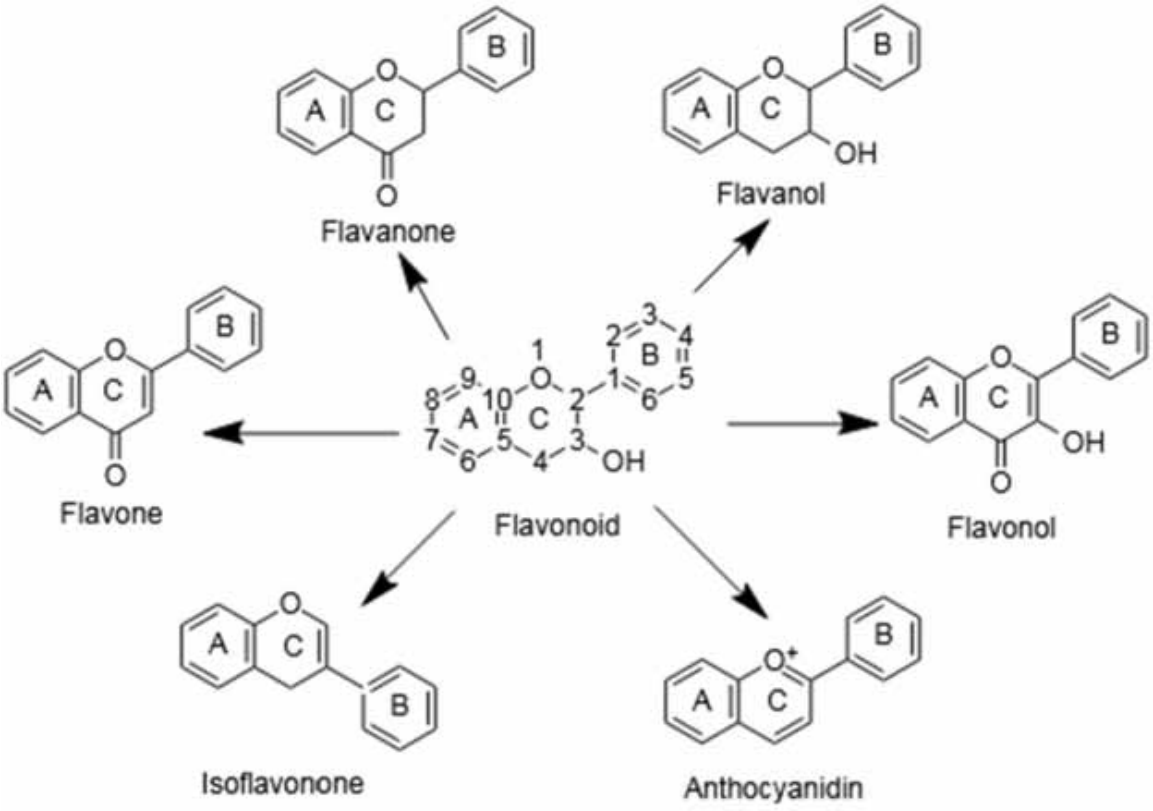
The flavonoids are characterized by basic structure called flavan indicated at central position in the figure. The flavan skeleton is composed of two aromatic rings which may be designated as ring A and ring B that is linked by a heterocyclic pyran ring, C. Thus, it is a complex organic molecule of 15-carbon phenylpropanoid chain having C6-C3-C6 carbon arrangement. Degree of oxidation in pyran ring (ring C), and hydroxylation and alkylation in benzene rings (ring A & ring B) determine the type of flavonoid.

Different flavonoid subclasses are structurally modified form of basic flavan structure which are further differently modified by hydroxylation and alkylatiom at one or more location in the both benzene rings (ring A and ring B) and pyran ring (ring C).

Aglycone (b.) is easily absorbed in the intestine while flavonoid glycoside (a.) needs to be hydrolysed to form aglycone before absorption. Only fraction of flavonoid glycoside is absorbed in the intestine while most of the glycosylated flavonoids are absorbed in the colon. Glucoside flavonoids are absorbed in the small intestine.

After absorption, all flavonoid enter liver through hepato-enteric circulation where they are conjugated with glucuronide or sulfate to form glucoronide flavonoid or flavonoid sulfate or modified into its methylated form by phase II enzymes such as sulfotransferase (SULT), uridine-5′-diphosphate (UGT)

Figure 2. Types of dietary flavonoids



and others through the process of glucuronidation, sulfation and methylation. These modified flavonoids are either secreted in the bile and later degraded in colon by intestinal bacteria or excreted through urine.

ROS is generated in inner membrane of mitochondria as superoxide anion ($O_2^{\bullet-}$) as a by-product of electron transport system. Superoxide anion thus produced is released into cytosol via mitochondrial permeability pore (MPTP) where it converted into hydrogen peroxide (H_2O_2) with the help of copper/zinc superoxide dismutase (Cu/Zn SOD). Those superoxide anions which enter mitochondrial matrices are converted into H_2O_2 with the help of manganese superoxide dismutase (Mn SOD). H_2O_2 thus produced is readily diffused to cytosol where they are either converted into 2 molecules of water ($2.H_2O$) and a molecule of oxygen (O_2) with the help of catalase enzyme or hydroxyl radical ($^{\bullet}OH$) through Fenton reaction. Some of the superoxide ions are also produced in response to cytokine signaling mediated by tumor necrosis factor (TNF)-α and platelet-derived growth factor (PDGF) with the help of NAPH oxidase (NOX). Hydroxyl radicals are highly reactive ions which are able to damage biomolecules such as proteins, DNA and lipid. Flavonoids can inhibit SOD, NOX and xanthine oxidase (XOD), while activate anti-oxidant enzymes, such as catalase, glutathione peroxidase (GPX) and peroxiredoxins (Prx). Flavonoids also activate metal chelation of superoxide anions.

Free radicals or ROS are produced both by extrinsic and intrinsic pathways. In response to death signal from external source, ROS is produced by extrinsic apoptotic pathway, whereas in response to internal stimuli, ROS is produced by intrinsic apoptotic pathway. ROS activates caspase 3, 6, 7 through

Figure 3. Overview of major class of flavonoids

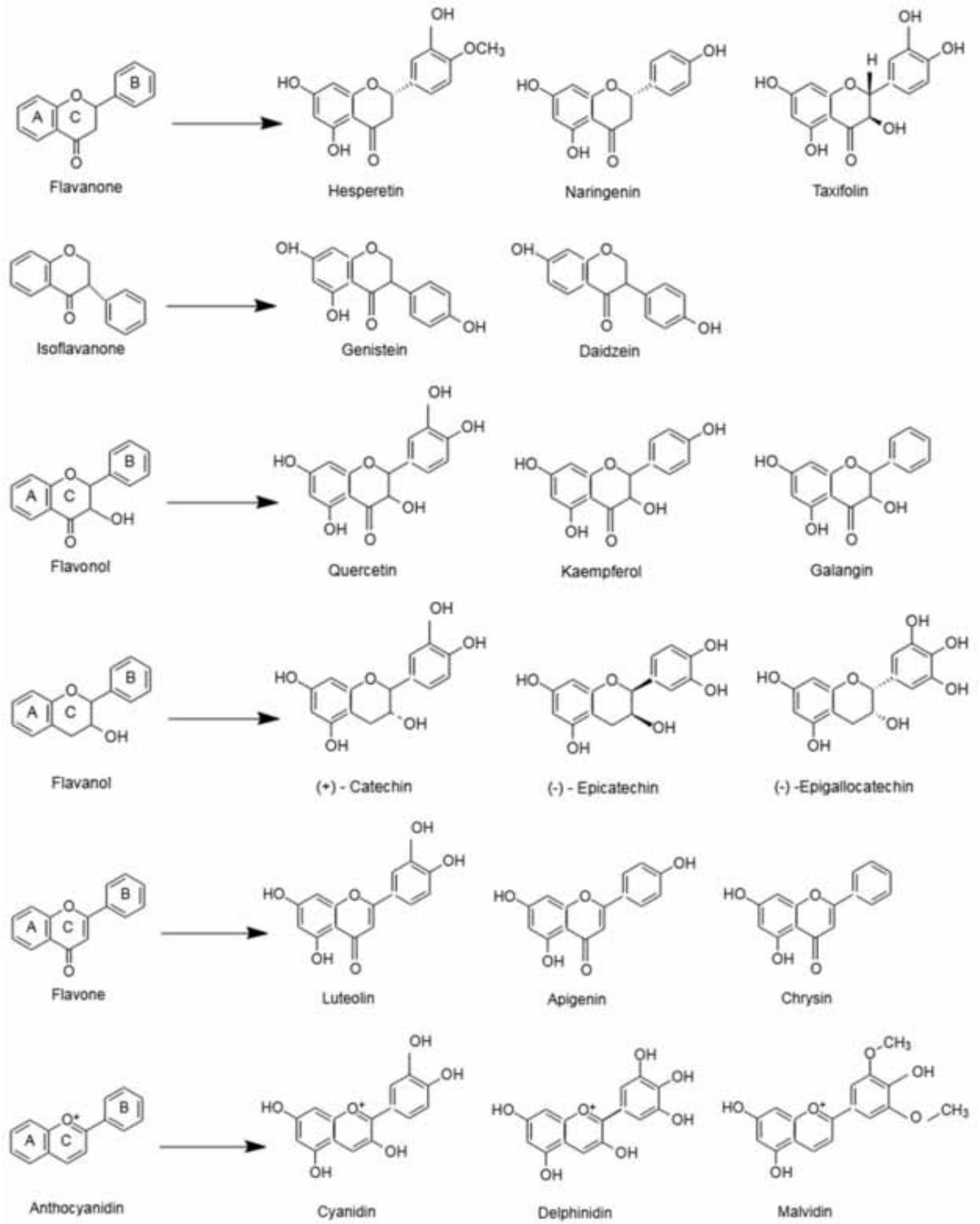


Figure 4. Glycosylated flavonoid and aglycan flavonoid

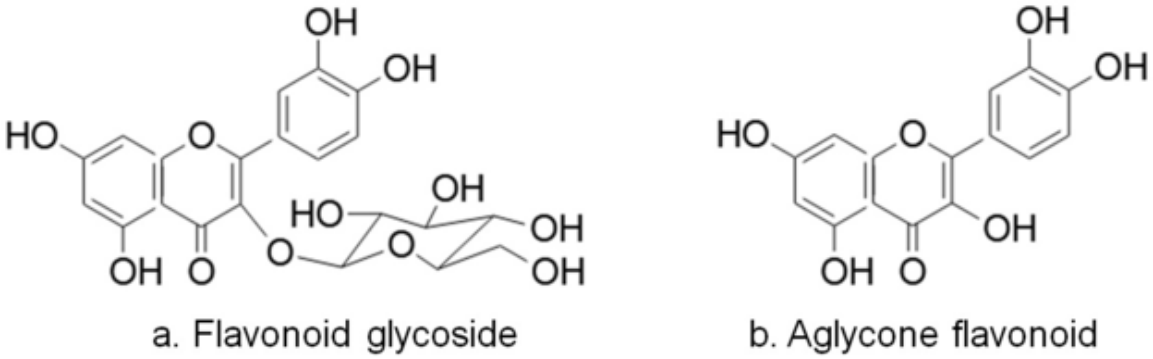
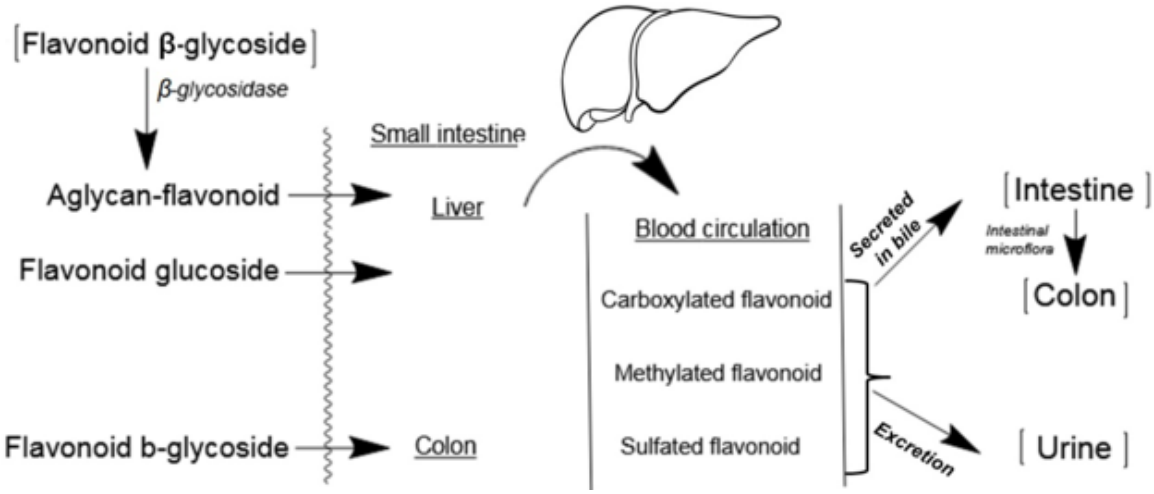


Figure 5. Metabolism of flavonoid in human



the activation of caspase 9 that finally results in apoptosis. Flavonoids increases the expression of p53 with simultaneous decrease in Bcl-2 that causes up-regulation of cytochrome C. Cytochrome stimulates caspase 3, 6, 7 through caspase 9 that leads to apoptosis of tumor cells.

Flavonoids exert anti-proliferative effect by regulating cell cycle that leads to cell cycle arrest at S phase while flavonoid-mediated regulation of PI3K results in cell cycle arrest at G2/M phase of cell cycle thereby inhibiting the tumor cell proliferation and metastasis. Activation of caspases and up-regulation of ROS induces DNA fragmentation and apoptosis of tumor cells.

Flavonoids inhibit the expression of transcription factors that are crucial for formation of pro-inflammatory microenvironment by up-regulating the expression of pro-inflammatory cytokines and down-regulating the expression of anti-inflammatory cytokines. They also suppress inducible enzymes and kinases to inhibit the formation of pro-inflammatory or pro-tumor microenvironment.

Figure 6. Effect of flavonoid in ROS

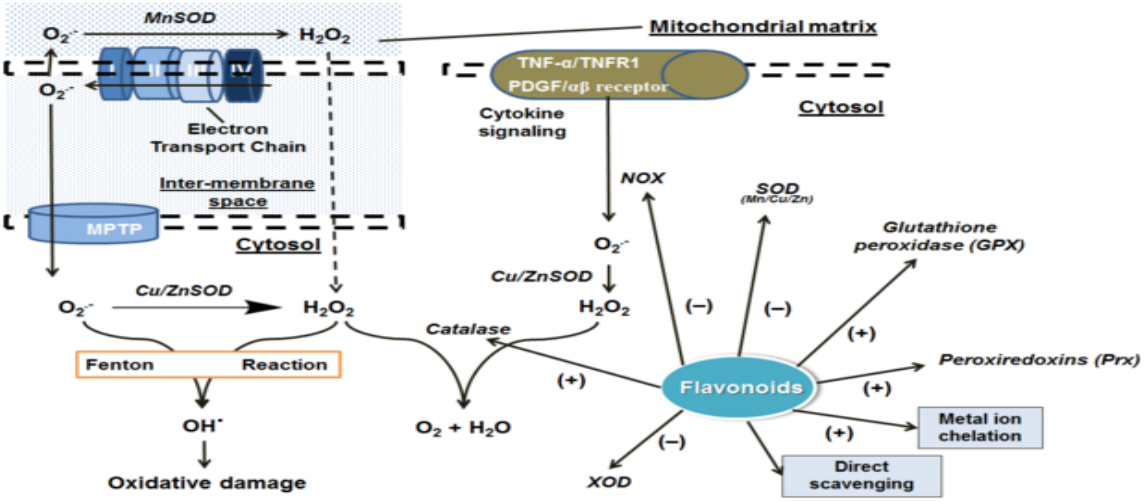


Figure 7. Effect of flavonoids on apoptosis of tumor cells

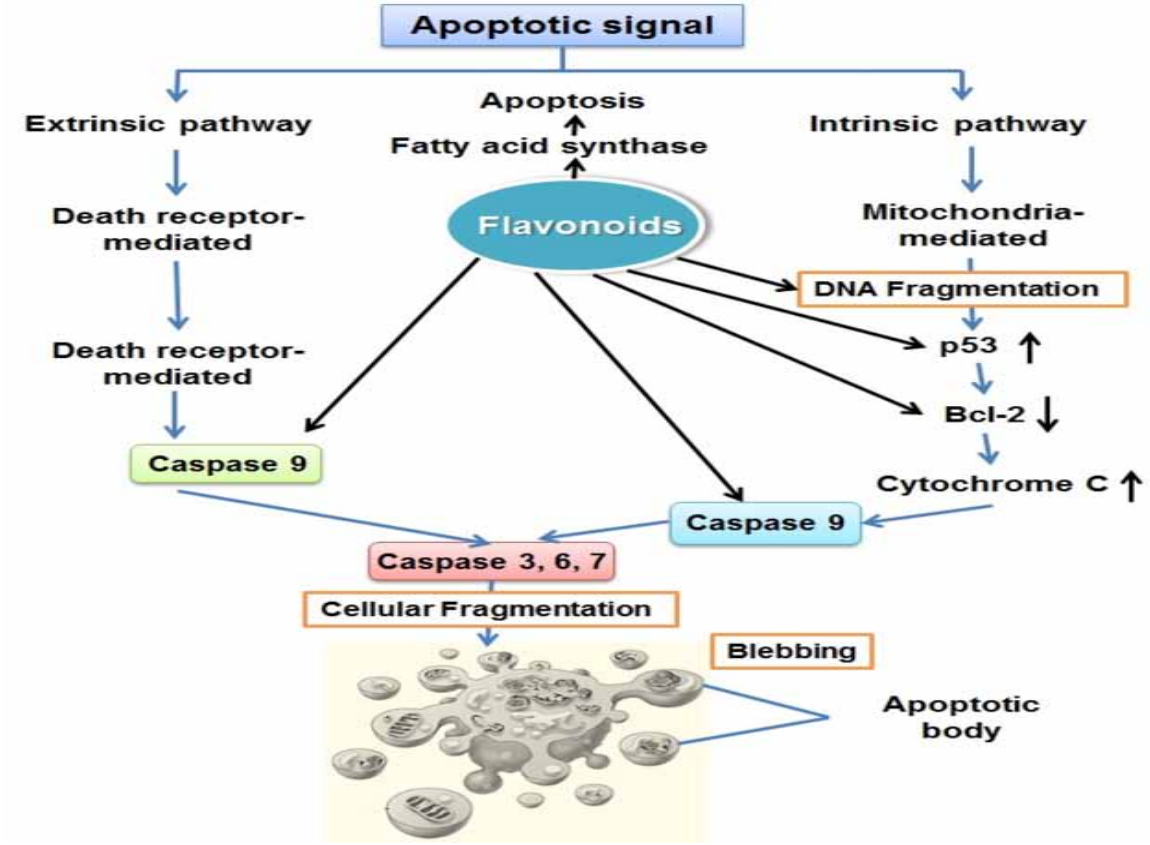


Figure 8. Regulation of tumor cell proliferation by flavonoids

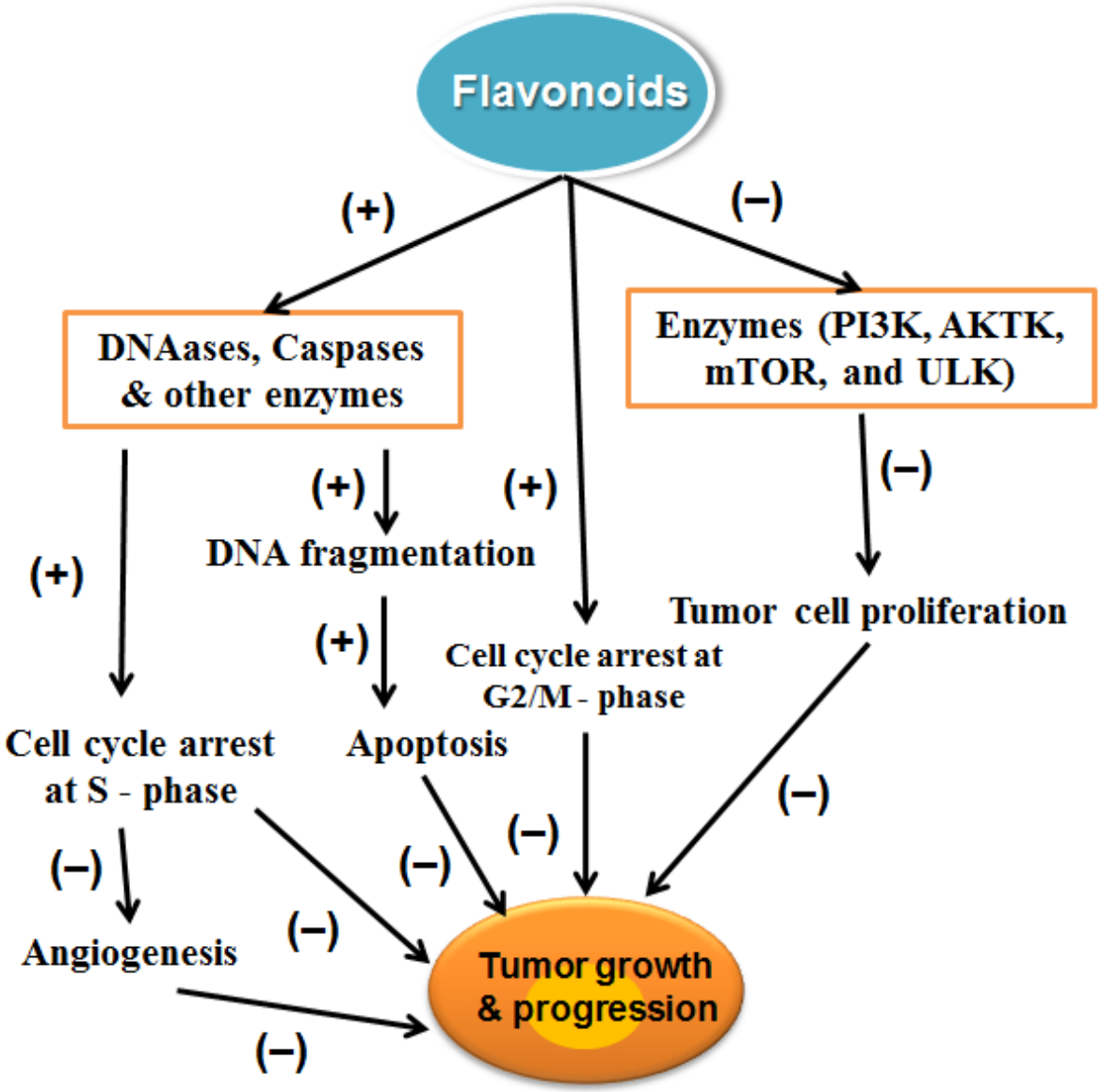
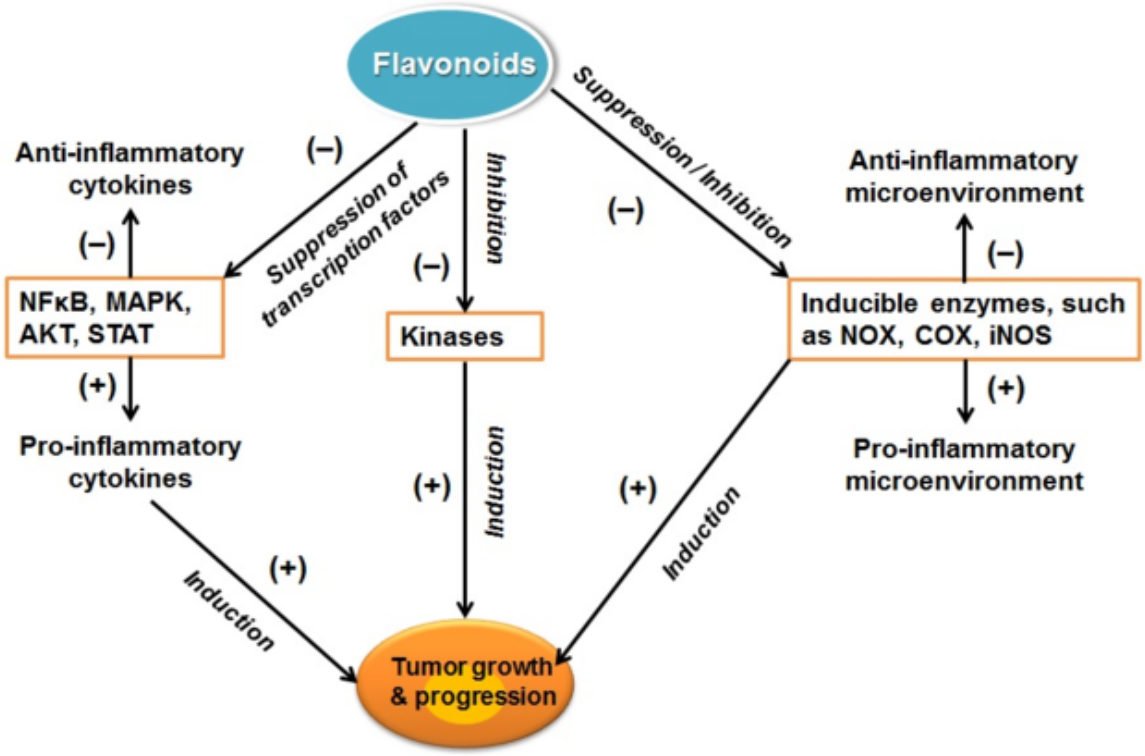


Figure 9. Modulation of inflammatory microenvironment by flavonoids



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Chapter 16
Alkaloid Containing Natural Products for Therapeutic Use in Cancer

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ABSTRACT

The diverse nature of chemotherapeutic agents obtained from natural compounds has led to the uncovering of several novel anti-cancer mechanisms, which are crucial for their spectrum of activity. Alkaloids are a class of organic compounds that have contributed to developing drugs used to treat a wide array of illnesses. Several alkaloids extracted from natural sources have demonstrated anti-cancer properties against various types of cancer when tested using cell culture, preclinical, and clinical studies. Chemotherapeutic compounds obtained and synthesized from natural sources of alkaloids might be the best possible solution for reducing the harmful side effects of currently utilized anti-cancer products. The chapter provides a thorough and critical assessment of naturally occurring alkaloids with anti-cancer properties and an overview of some of the alkaloid-containing natural compounds that have demonstrated significant anti-proliferative activity and progressed to preclinical and/or clinical trials in the context of future drug development for cancer therapy.

INTRODUCTION

Nowadays the frequency of cancer is increasing regardless of the age range and has become the leading cause of mortality across the world. Mutations in the DNA, which guide the cells how to grow and divide, set the stage for cancer. This mutation can occur for both genetic and environmental factors. Normally

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cells are able to fix most of the mutations in their DNA, but when cells fail to repair this, the mutation that is responsible for the uncontrolled proliferation of the cells becomes malignant (Prakash et al., 2013).

Cancer and its Probable Causes

As per the WHO, *cancer* is defined as "a large group of diseases that can start in almost any organ or tissue of the body when the abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to the other organs" ("The Global Challenge of Cancer," 2020). Early epidemiological studies have identified exposure to occupational agents like soot, x–rays, shale oil, chromate, and coal tar, and non–occupational agents like tobacco snuff were significant causes of cancer (Blackadar, 2016). However, as of late, the significant causes of cancer have been identified as tobacco and viral infections like HIV, hepatitis B, Epstein–Barr virus. Other minor factors that lead to cancer development are poor diet, excessive consumption of alcohol, obesity, exposure to ionizing radiation, genetic disorders like Lynch syndrome, and excessive sun exposure. In addition, high-dose chemotherapy, hormonal drugs, immune-suppressing drugs, and exposure to radioactive materials like radon have also been implicated with an increased risk of cancer (Saini et al., 2020).

Global Scenario of Cancer

The most typical source of death after cardiovascular diseases globally is cancer. According to the World Health Organization, cancer is a leading cause of one in six deaths ("The Global Challenge of Cancer," 2020). The worldwide incidence of cancer is approximated to have gone up to new cases of 19.3 million and deaths of 10.0 million in the year 2020 (Sung et al., 2021). Globally, one in five individuals experiences cancer at some point in their life, and one in eight men and one in eleven women pass away from cancer.

Female breast cancer is reported as the most common type of cancer worldwide in a current report. Leukemia and pancreatic cancer are other common forms of cancer reported (Ferlay et al., 2015). Cancers of the lip and oral cavity account for the 16th most common form of cancers in the world. In South Asia, Pakistan had the highest incidence of cancer of the lip and oral cavity, 12.2 individuals per 100,000 people, followed by Bangladesh, 9.5 individuals per 100,000 people, and India, 9.1 individuals per 100,000 people (Bray et al., 2018).

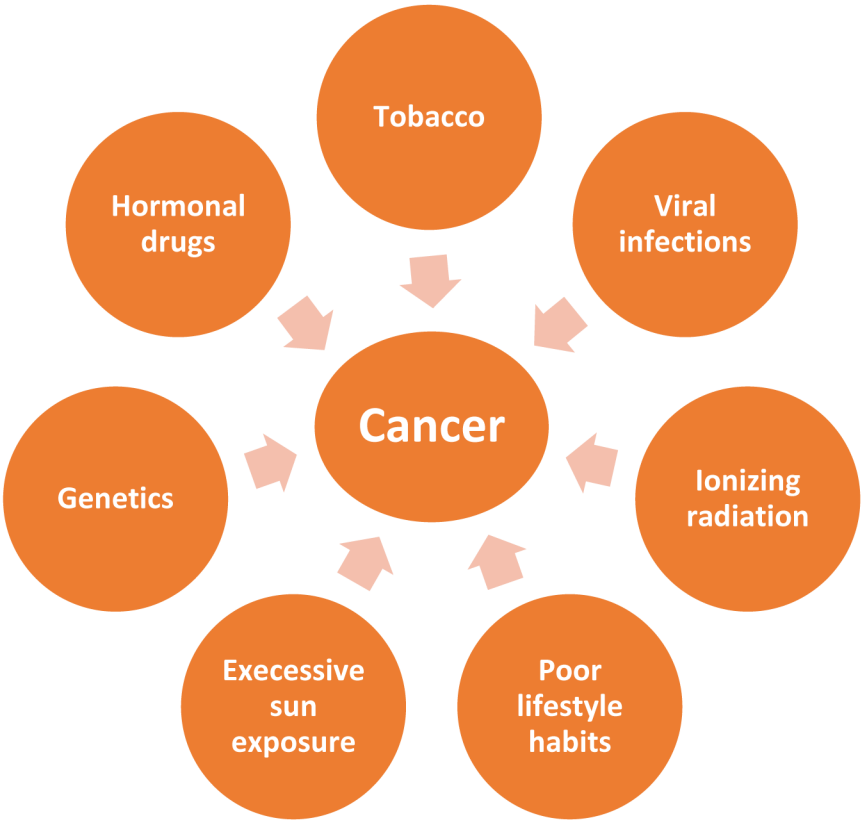
Statistically, across the globe, the middle-income and the high-income countries have been suffering from cancer of the respiratory tract, which is tracheal, bronchus, and lung cancer, which raises death tolls there. It varies in the countries with lower-income status from colon and rectal cancer, liver cancer, cervical cancer, stomach cancer to breast and prostate cancer, and shuffling the list (D. Brown et al., 2021).

According to the World Health Organization (WHO), cancer's deadly strike will affect one in five men and one in six women before they reach the age of 75. Again, one in eight men and one in twelve women will be deceased from the disease. There is a chance of being affected by cancer within 2040 of around 27 million people (Boyle & Levin, 2008).

Methods of Diagnosis and Conventional Treatment Strategies of Cancer

There are several diagnostic methods and many diagnostic tools with technological advantages available for detecting cancer. However, some cancers, especially lymph nodal cancers, are difficult to diagnose in

Figure 1. Probable Causes of Cancer



their stage or type. Therefore, expert opinion is necessary to diagnose the exact stage or type of cancer in such cases (Y. Zhou et al., 2017).

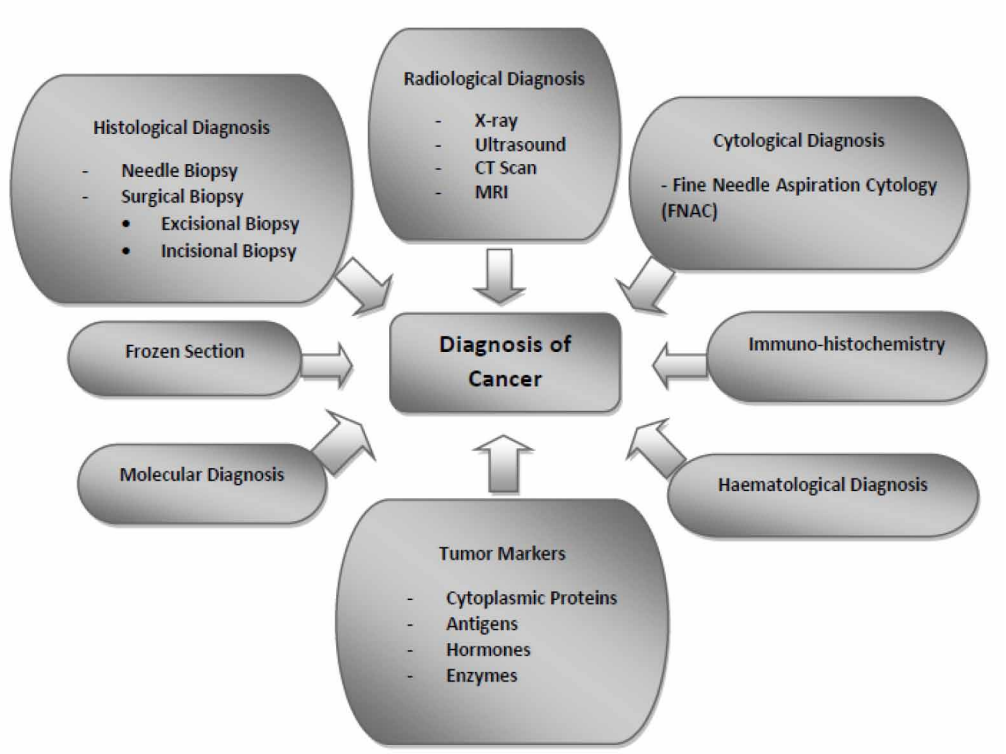
The following figure depicts the methods of diagnosing cancer:

There are several strategies for the treatment methods available for cancer like surgery, radiotherapy, chemotherapy, targeted therapy, hormone therapy, photodynamic therapy, immunotherapy, stem cell transplant among which chemotherapy is the most common therapeutic approach. Radiotherapy and surgery basically kill or remove cancerous cells by targeting only a specific body part. But in chemotherapy, chemotherapeutic agent works across the entire body of a patient with lower adverse effects to effectively prevent the metastasis process through which spreading of cancerous cells from their primary site to the distant parts of the body occurs (Pucci et al., 2019). There is still a pressing need for more effective solutions considering the high morbidity rate and enormous economic impact as cancer treatment.

Rationale of The Anti-Cancer Natural Products

Natural products, which are relatively pure substances isolated from plants, have traditionally been a primary source of disease treatment formulations. Using natural products for controlling cancer are considered as more biologically friendly and better source in the field of drug discovery than synthetic

Figure 2. Diagnostic Methods of Cancer



products because they are thought to have co-evolved with their targeted sites in biological systems (Mishra & Tiwari, 2011).

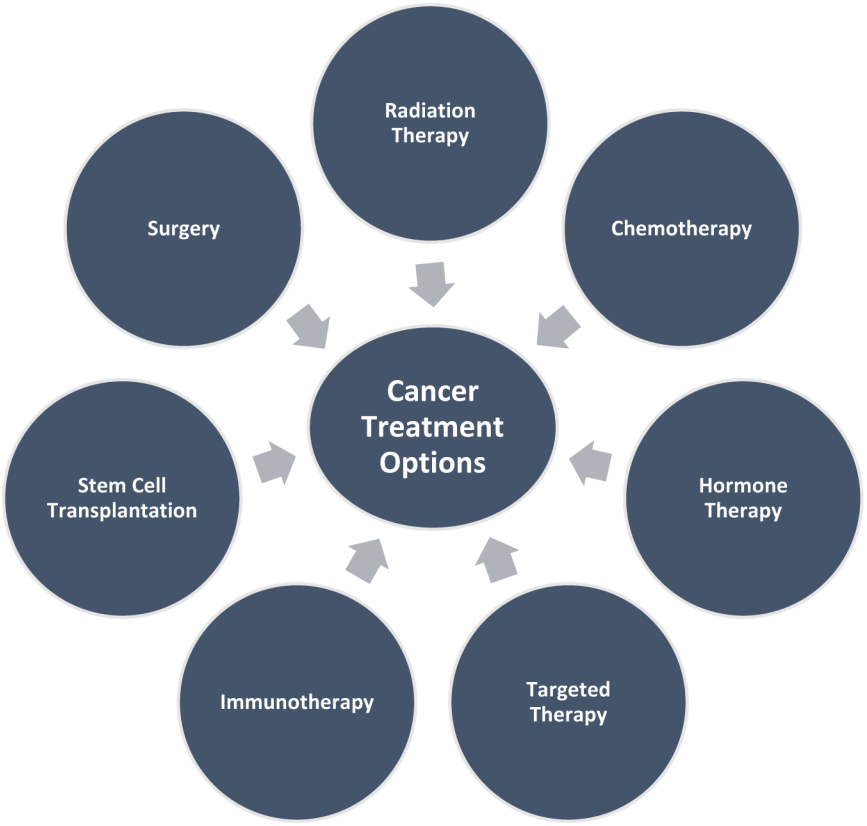
Statistics showed that around 80% of the world's population relies on botanicals to treat a variety of diseases (El-Saber Batiha et al., 2020). Consequently, the pharmaceutical industry has lately concentrated on developing new medic therapeutic agents derived from plants as they contains a variety of therapeutic agents, notably alkaloids, which in fact are the most significant bioactive components in plant.

Investigating the kingdom of plants to find out anti-cancer compounds led to the revelation of chemo-therapeutic potential of alkaloids (Yuan et al., 2016). Alkaloids mostly are synthesized in higher plants, for instance- those in the families of Menispermaceae, Papaveraceae, Ranunculaceae, Loganiaceae and Leguminosae, as secondary metabolites for defensive purpose (J.-J. Lu et al., 2012). Sometimes their yield amount is high in fruits, seeds or leaves while sometimes in bark or root based on the tree tissue and species. However, the yield is usually low, resulting in over-exploitation of the natural population for the compounds (Isah, 2015).

The improvements in chemotherapy made in the twenty-first century are the outcome of significant contribution from chemotherapeutic alkaloids obtained from natural sources than from any other form of life, and they have resulted in the extended survival of patients suffering from various types of cancer. These achievements have been made possible due to the screening and identification of several chemotherapeutic alkaloids from plant species and advancement of technology (DeVita & Chu, 2008).

Alkaloids have shown numerous effective biological functions, to exemplify- ephedrine exhibit relieving action for asthma, morphine has analgesic (painkiller) effects and vinblastine showed anti-

Figure 3. Conventional Treatment Options for Cancer



cancer activities (M. R. Lee, 2011). As a first NME (new molecular entities) from plant, the alkaloid "morphine" was commercialized in 1827 (Patridge et al., 2016). Following the discovery of morphine, further active compounds such as paclitaxel, an alkaloid derived from *Taxus brevifolia*, were discovered (Junjua & Ahmed, 2015). By binding to β-tubulin, paclitaxel helps to stabilize the microtubule polymer, preventing the dynamic microtubule disintegration process required for proper mitotic spindle construction and chromosomal segregation during cell division (Snyder et al., 2001).

Paclitaxel is being used to treat a variety of cancer, such as breast, ovarian, pancreatic, lung, Kaposi's sarcoma caused by the human herpesvirus-8 and so on. Unlike paclitaxel, another alkaloid vinblastine, which was isolated from *Catharanthus roseus* and considered as broad spectrum chemotherapeutic drug, binds to a different location on β-tubulin to block microtubule polymerization that results in cell cycle arrest in M-phase (Nejat et al., 2015). There are tons of more evidences on the efficacy of alkaloids as chemotherapeutic agents. Camptothecin, a well-known topoisomerase-I inhibitor, isolated from *Camptotheca acuminata* has already been turned into chemotherapeutics with great success (Min Huang et al., 2007).

The bis-benzyl-isoquinoline alkaloid tetrandrine, isolated from *Stephania tetrandra* roots, has been used in China for decades for the treatment of patients suffering from autoimmune disorders, silicosis, inflammatory pulmonary diseases, hypertension and cardiovascular diseases. It also has therapeutic potential in chemotherapy. Tetrandrine attacks tumor cells by inhibiting proliferation and inducing apoptosis

on cancer cell lines including, human hepatoma HepG2 (Yoo et al., 2002), human lung carcinoma A549 (J. H. Lee et al., 2002), human colon cancer HCT-116 (Meng et al., 2004), and human leukemic U937 (Y. J. Chen, 2002) as well as on primary cancer cells obtained from pleural fluids and ascites, such as A-Li40, A-Ga31, A-Co20 and P-Lu18 cells, isolated from liver, gastric, colon and lung cancer patients, respectively (Liu et al., 2008).

The present chapter thoroughly discuss about the chemotherapeutic activity containing plant derived alkaloids along with their mechanism of action, structure activity relationships to reveal their possibilities of becoming potential therapeutic agents in the field of oncotherapy.

ALKALOIDS WITH ANTICARCINOGENIC ACTIVITY

1. Vinca Alkaloids

Vinca alkaloids are important cancer fighting agents that act by eliciting anti–mitotic and anti–microtubule action. This group comprises four major alkaloids namely, vincristine (VCR), vinblastine (VBL), vinorelbine (VRL), and vindesine (VDS). These are extracted from the perennial tropical plant, *Catharanthus roseus* or periwinkle and constitute the oldest group of plant alkaloids with anti-cancer activity (Moudi et al., 2013).

Despite all four alkaloids being tested in the clinical trials, the United States has approved only VCR, VBL, and VRL for use in clinical settings (Rowinsky, 2003). In addition to these, a fluorinated vinca alkaloid called vinflunine has been also approved for therapeutic use in Europe (Schutz et al., 2011).

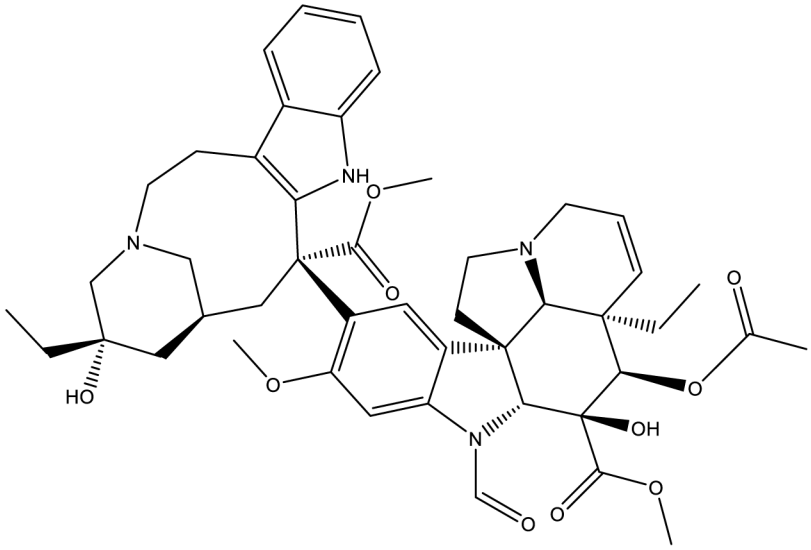
Chemically, all the vinca alkaloids are dimeric structures consisting of two large rings: catharanthine (indole nucleus) and vindoline (dihydroindole nucleus). VCR and VBL differ in the group substituted at the R1 position of the vindoline nucleus, with the former possessing a formyl group while the latter possessing a methyl group in its place. VRL is a semi-synthetic derivative of VBL that differs by the modification of the catharanthine ring. This modification has altered its pharmacokinetic properties, making it more lipophilic when compared to other vinca alkaloids.

In contrast to these, VDS has two structural variations at the R2 and R3 positions of the vindoline ring. Modification of the catharanthine moiety by the introduction of two fluorine atoms at the 20^{th} position resulted in the production of the synthetic analogue vinflunine (Rowinsky, 2003). Despite their structural similarity, these alkaloids vary in their spectrum of activity and toxicity profiles.

a. Mechanism of action

Cytotoxic action of vinca alkaloids occurs due to their interaction with the β-tubulin at the vinca domain, a region adjacent to the GTP-binding site of the tumor cells. At the therapeutic concentration, this interaction disrupts the mitotic spindle formation and leads to apoptosis by arresting the metaphase (M) of the cell cycle (Naeem et al., 2017). Vinca alkaloids generally destabilize the dynamic microtubule cytoskeleton which consists of α– and β–tubulin dimers. This network is also responsible for transporting and positioning the intracellular organelles (endosomes, autophagosomes, lysosomes, etc.) as well as for the separation of the chromatids in the dividing cells during the anaphase of mitosis. The dissolution of the mitotic spindle and subsequent anti-mitotic action depends on the concentration of the vinca alkaloid used.

Figure 4. Structures of Vinca Alkaloids



Vincristine

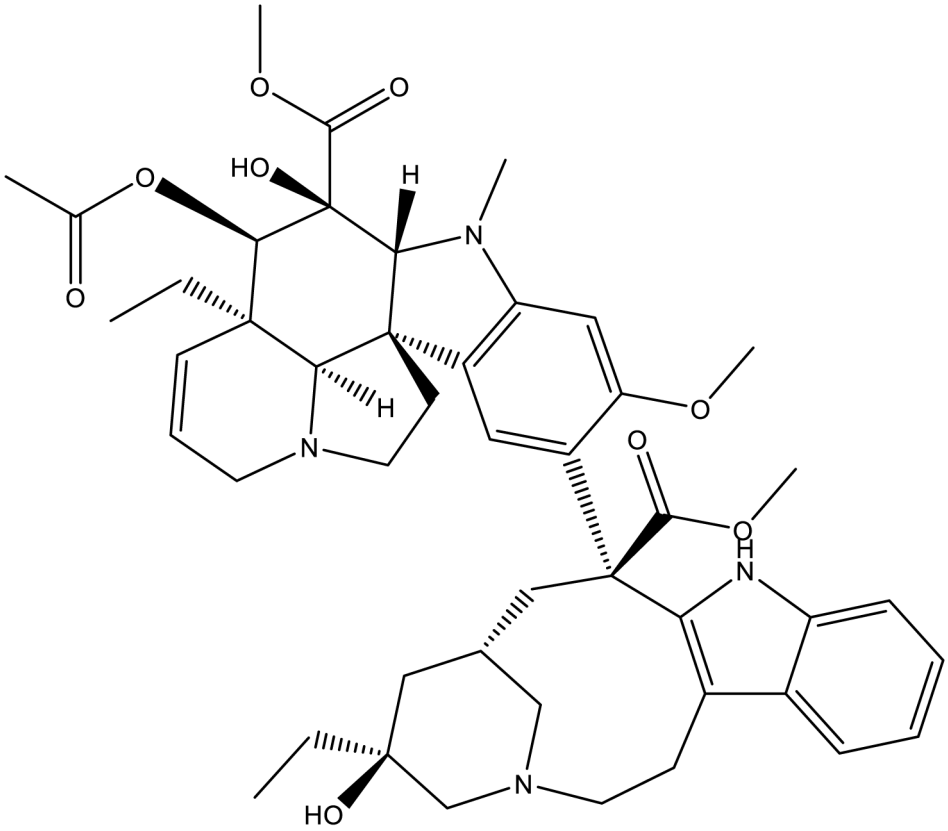
At lower concentrations (<1μmol) these alkaloids inhibits microtubule dynamics, spread the microtubules into spiral proto-filaments and lead to microtubule disintegration. However, at higher concentrations (>1 to 2μmol), it induces microtubule de-polymerization by weakening the interaction between these proto-filaments and results in the formation of para-crystals. Regardless of the pathway followed, the vinca alkaloids result in mitotic block by the spindle assembly checkpoint that in turn inhibits the proliferation of the tumor cells (Naeem et al., 2017).

Cell death following the continuous usage of these microtubule poisons is not just attributed to mitotic arrest. Instead it brings about this effect by targeting the highly dynamic cytosolic organelles called lysosomes. Vincristine was found to increase the size of the lysosomal compartment by merging the pre-existing lysosomes and by the defective turnover of these organelles by exocytosis or autophagy. This is succeeded by the increased permeation of the lysosomal membrane which in turn results in the release of cathepsin proteases in the cytosol and finally leads to the apoptosis of the tumor cells. In addition to these changes, lysosomal permeation was also found to activate the apoptosis regulator protein, Bax (Bcl–2–associated X protein) and trigger the intrinsic apoptosis pathway as a secondary event (Groth-Pedersen et al., 2007).

Despite having a similar mechanism of action, these alkaloids vary in their pharmacokinetic parameters. Exposure of the human cancer cells to VCR for a shorter duration has a greater potency as it is largely retained in the cells (Kumar AS., 2016). The structural modification of the catharanthine ring makes VRL more lipophilic and this is associated with less neurotoxicity in contrast to other vinca alkaloids.

This anomalous trait of VRL is attributed to its highly lipophilic nature which renders it more effective in disrupting the microtubules of the mitotic spindles rather than the axonal microtubules (Koul et al., 2013). VRL also showed more rapid cellular uptake and metabolism in isolated human hepatocytes unlike

Figure 5.



Vinblastine

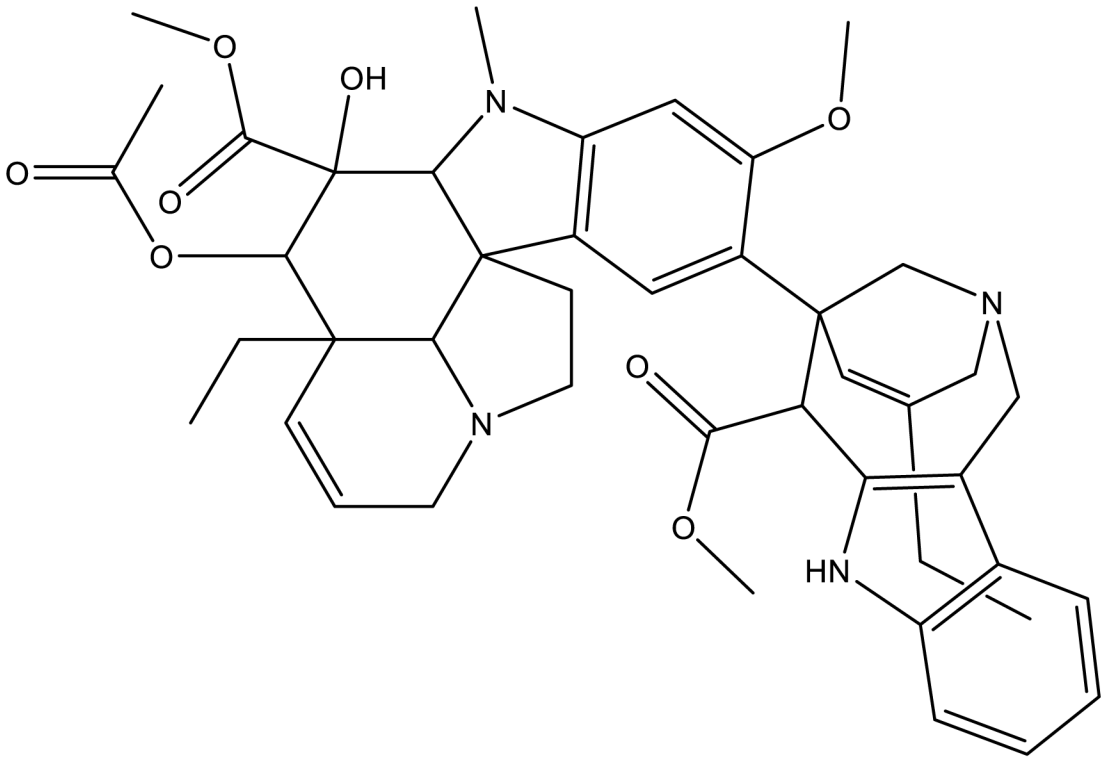
the other members of this group (Groninger et al., 2002). Vinflunine also exhibits reduced neurotoxicity as it is has a very weak affinity with the tubulin and forms fewer spiral filaments (Bennouna et al., 2008).

b. Pharmacological Uses and Toxicities

VCR is predominantly used to treat pediatric malignancies and acute lymphocytic leukemia in both children and adults. It is also an essential component in the chemotherapy regimens employed for the management of Hodgkin's and non-Hodgkin's lymphomas. VBL, in contrast, is widely used both alone and in combination with other anti-cancer agents to treat germ cell malignancies, advanced lymphomas, Kaposi's sarcoma, metastatic urothelial carcinoma, and other types of breast, brain, and bladder tumors.

Lymphoid malignancies and lymphoblastic leukemia are effectively treated by using vinflunine, as this arrests the cell cycle of the tumor cells at the G2/M checkpoint. Vinca alkaloids are a mainstay component in the chemotherapy of a wide range of malignancies but their use is limited owing to toxicity and resistance. The myelo-suppression produced by these agents are reversible, but the neurotoxicity associated with them is not. This generally causes permanent damage to the individual by inducing

Figure 6.



Vinorelbine

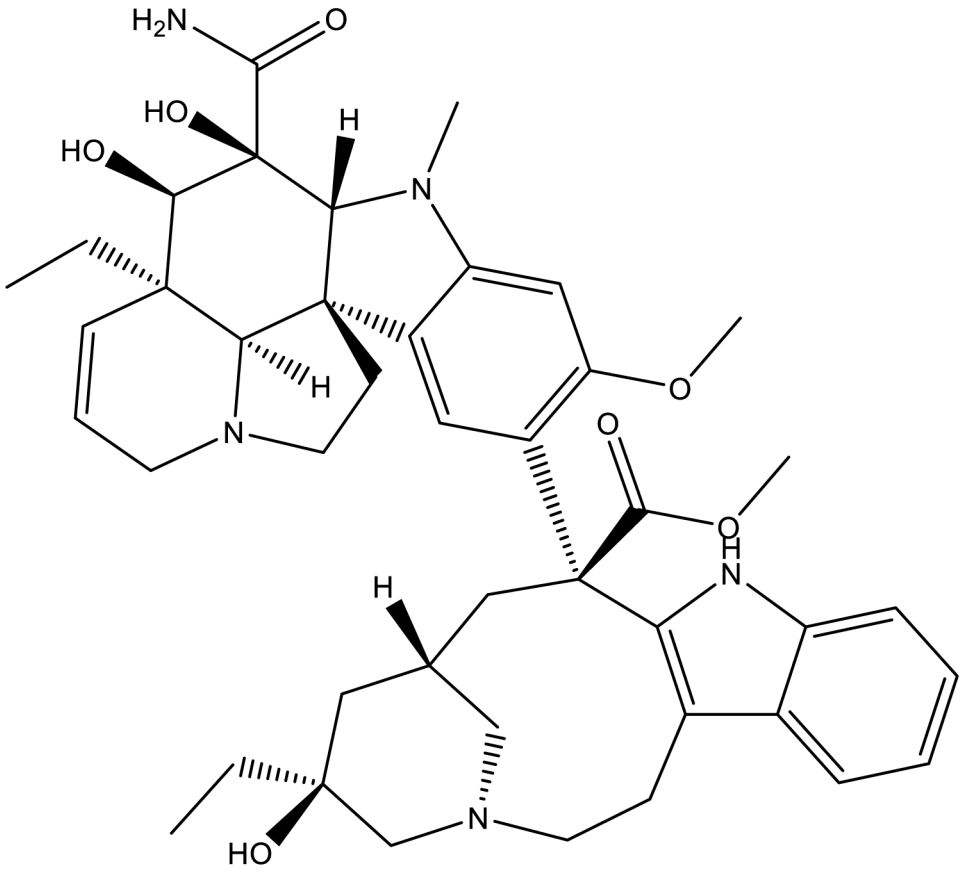
neuropathies. In an effort to combat this side effect, several new agents are now being developed with the rationale to elicit anti-mitotic activity with minimal to no neurotoxicity (Kruczynski & Hill, 2001).

2. Meridianins

Meridianins are a family of indole alkaloids that have been isolated from a marine organism called *Aplidium meridianum*. This organism is an Ascidian that usually resides in the South Atlantic region. This family comprises the naturally occurring alkaloids namely Meridianins A-G that possess a pyrimidyl-substituted indole ring (Imperatore et al., 2014). The natural meridianins have a promising kinase inhibitory scaffold and are either brominated or hydroxylated at the 3rd position of the substituted indole nucleus.

They elicit antitumor activity by inhibiting the protein kinases involved in the regulation of cell cycle and neuronal functioning. The substituted meridianin skeleton acts by interfering with the activity of kinases such as cyclin-dependent kinases (CDKs), glycogen synthase kinase-3, cyclin nucleotide-dependent kinases, and casein kinase 1 (Fresneda et al., 2001). The anti-proliferative activity of these agents depends on the substitution of the basic nucleus and this is well-established by weak inhibitory activity of the unsubstituted Meridianin G.

Figure 7.



Vindesine

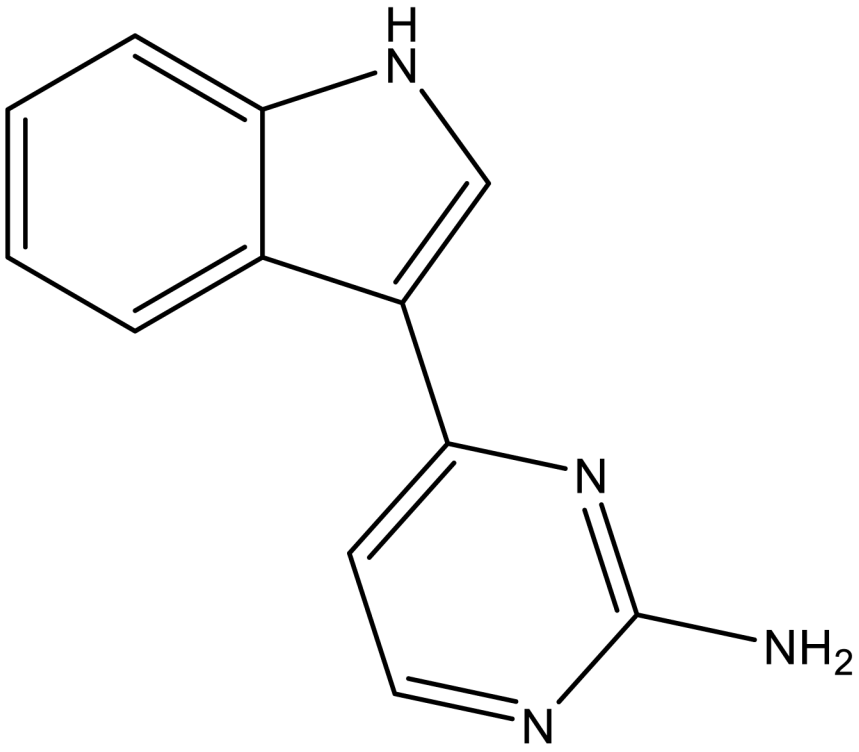
Another significant trait of these alkaloids is the bromination of the indole nucleus as this correlates with the cytotoxic effect (Gompel et al., 2004). Meridianin A bolsters this principle as the absence of a bromine substituted nucleus in this alkaloid has resulted in its lack of cytotoxic effect albeit it having a considerable good inhibitory effect on the protein kinases.

The mono-brominated meridianins (meridianin C and D) show relatively greater potency when compared to the di-brominated meridianin F. Meridianin B-F have successfully established their cellular effects on various human tumor cell lines including breast, cervix, liver, and brain tumor cell lines (Radwan & El-Sherbiny, 2007).

3. Nortopsentins

Nortopsentins A, B and C are an important class of bis-indolyl alkaloids that are isolated from the deep-sea sponges, *Spongosorites ruetzleri*. These metabolites have remarkable cytotoxic activity that has been demonstrated by in vitro studies against P388 murine leukemia cell line (Ercolano et al., 2019). The

Figure 8. Structure of Meridianin G



anti-proliferative activity of nortopsentins showed promising results when evaluated against a panel of over 60 human cancer cell lines that have been derived from non-small cell lung cancer, colon cancer, ovarian cancer, prostate cancer, breast cancer, and melanoma among others (Kamel et al., 2020).

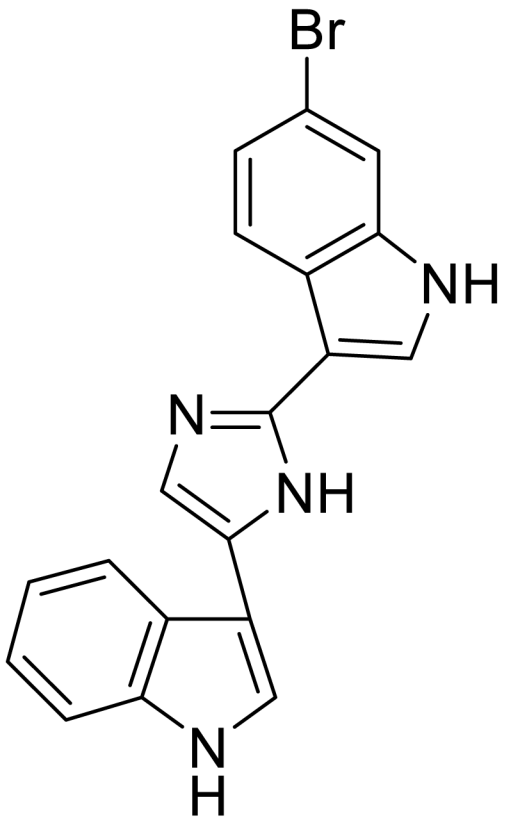
Structural manipulation of the basic imidazole ring of these metabolites has given rise to a number of analogues that demonstrated significant anti-cancer activity at micromolar range. Replacement of the imidazole ring with five–membered heterocyclic ring systems such as pyrazole, furans, pyrroles, oxazoles, and 1,2,4–thiadiazoles have resulted in the generation of newer molecules with considerable antitumor activity.

The synthetic derivatives of nortopsentin that were produced by incorporating a naphthyl or 7–azaindolyl group in the place of an indole unit have shown good anti-cancer activity. These agents when tested with breast cancer cell lines (MCF7 cells) showed pro-apoptotic activity without exerting any necrotic effects. Furthermore, these derivatives led to the perturbation of the cell cycle at the G0/G1 phase and S phase (Synthesis phase), and induction of the cells to shift towards early apoptosis (Di Franco et al., 2021).

4. Camptothecin

The anti-cancer activity of camptothecin (CPT) is a key area of interest to researchers as this led to the discovery of newer targets for anti-cancer drug discovery. CPT is a penta-cyclic alkaloid that has been

Figure 9. Structure of Nortopsentin A



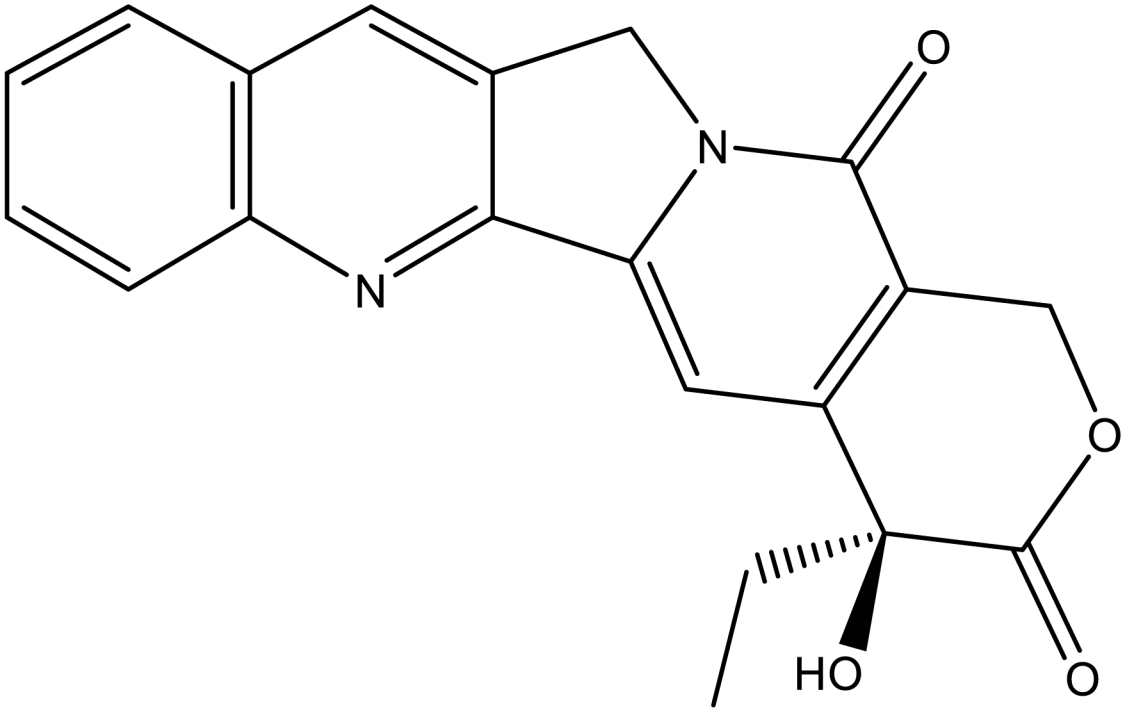
extensively studied for its cytotoxic effect in stomach, colorectal, bladder, and head & neck cancer. This molecule inhibits an enzyme called Topoisomerase-I (Top1) that is essential for relaxing the supercoiled DNA and cell replication. CPT binds to the Top1/DNA complex and prevents its dissociation during the S and G2 phases of the cell cycle which in turn results in the breakage of the DNA double strand and subsequent cell death (Wu et al., 2020).

Despite having a unique molecular target, the clinical studies of CPT were shelved in the 1970s owing to its toxic side effects such as myelo-suppression, gastrointestinal toxicities, and hemorrhagic cystitis (Li et al., 2017). In a bid to overcome these drawbacks, the structure of CPT was manipulated and several CPT-based analogues were designed. While a number of analogues targeting various oncogenic proteins were synthesized in the recent years, only two of them (irinotecan and topotecan) have received the approval for cancer treatment.

5. Paclitaxel

Paclitaxel (previously known as taxol) is a widely used anti-cancer agent that has been isolated from the bark and needles of *Taxus* species, especially *T. brevifolia*. This tricyclic diterpenoid alkaloid has been approved by the USFDA and exerts anti-neoplastic activity even at nano-molar concentrations and

Figure 10. Structure of Camptothecin



has been approved by the United States Food and Drug Administration (FDA) for treating a number of malignancies.

It stabilizes the microtubules by binding with the β-tubulin and results in formation of a defective mitotic spindle assembly. This makes it difficult for the cells to achieve the necessary metaphase spindle configuration that is essential for the mitotic division and prolongs the activation of the mitotic checkpoint.

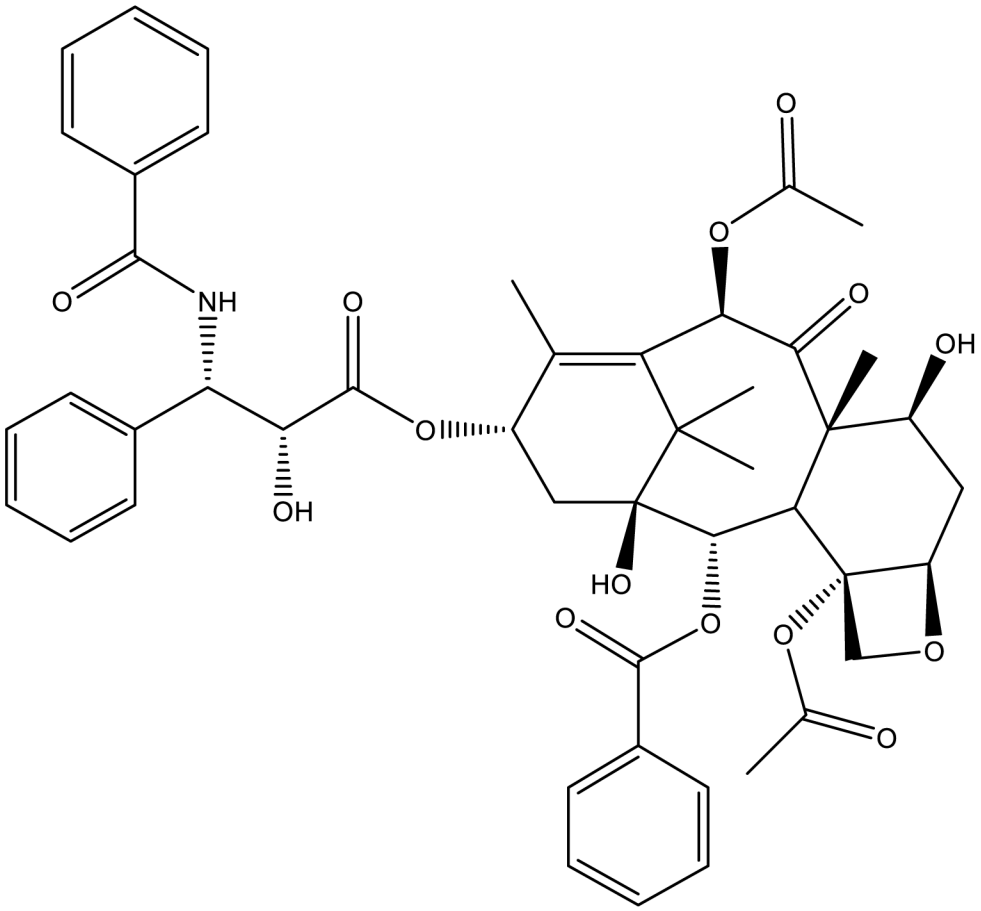
Unlike the vinca alkaloids that inhibit the assembly of the microtubules, taxol stabilizes the microtubules by promoting the assembly of tubulin and preventing their dissociation at the later stages of the cell cycle. Consequently, it triggers apoptosis or reversal to the G phase of the cell cycle and inhibits the proliferation of the tumor cells (Barbuti & Chen, 2015). In addition to this, taxol also acts by complementing the disruptions in the mitogen-activated protein kinase (MAPK) pathway or suppressing the activation of the nuclear factor-kappa B (NF-κB) pathway (Habli et al., 2017).

a. Pharmacological Uses and Toxicities

Taxol is frequently employed in the treatment of refractory ovarian cancer, advanced Kaposi's sarcoma, breast, colon, neck, esophageal, lung, and bladder cancer in addition to prostate melanoma and other solid tumors. Albeit having potent activity, this agent is administered with caution due to the toxic side effects it produces such as neutropenia, peripheral neuropathy, and cardio-toxicity.

Several strategies have been developed to facilitate the safe delivery of less toxic formulations of paclitaxel to the patients. This includes the generation of polymeric micelle nano-carrier formulations,

Figure 11. Structure of Taxol



congeners, pro-drugs such as Docosa-hexaenoic acid (DHA)-paclitaxel, polymer-drug conjugates like poly (l-glutamic acid)-paclitaxel and so on. These novel targeted-drug delivery systems are currently being researched across the globe and have demonstrated significant antitumor activity with a reduced exposure time to the healthy tissues (Isah, 2016).

b. Resistance mechanism

Another major caveat of paclitaxel is the development of drug resistance by the tumor cells through the cellular mechanisms. Drug efflux by the over-expression of an ATP-binding cassette (ABC) transporter called P-glycoprotein is one of the main mechanisms that is responsible for the decreased antitumor activity of paclitaxel. Mutation of α- and β-tubulin of the microtubules also confers resistance to paclitaxel without compromising the ability of the agent to bind to the microtubule network (Ganguly & Cabral, 2011).

Interestingly, the cells resistant to paclitaxel were found to be more sensitive to the microtubule destabilizing agents like vinca alkaloids owing to their affinity to free tubulin dimers. This unique trait

was attributed to the increased expression of β-tubulin isotypes (specifically β3 and β5) that lowered the levels of microtubules in the cells (Barbuti & Chen, 2015). In addition to being a part of the chemotherapy regimen, paclitaxel is also involved in tumor immunotherapy as it regulates various immune cells to induce an immune response to tumors.

The immune cells that are regulated by paclitaxel include effector T cells, natural killer (NK) cells, macrophages, regulatory T cells (Tregs), and dendritic cells among others. While the exact effect of the immunological effect of paclitaxel in cancer patients is yet to known, it is believed that this could provide long-term protection in cancer patients (Zhu & Chen, 2019).

6. Rohitukine

Rohitukine is an emerging alkaloid that acts by altering the mitogen-activated protein kinase (MAPK) pathway. This chromone alkaloid has been isolated from the leaves and stems of *Dysoxylum binectariferum*, and *Schumanniophyton magnificum*. It elicits antitumor activity by increasing the expression of the proteins p53 and caspase-9 with a simultaneous reduction in the levels of the anti-apoptotic protein, Bcl-2 (Safia et al., 2015).

The basic nucleus of rohitukine has been successfully altered to give rise to two congeners–Flavopiridol and P-276-00. These congeners elicited antitumor activity by inhibiting the cyclin-dependent kinases (CDKs) and blocking the progression of the cell cycle at the G1 (Gap1) and G2 (Gap2) phases. Although both the congeners are undergoing clinical trials to evaluate their antitumor activity, flavopiridol has been granted the orphan drug status for the treatment of chronic lymphocytic leukemia (J. R. Brown, 2005).

a. Antitumor Effect of Synthetic Congeners

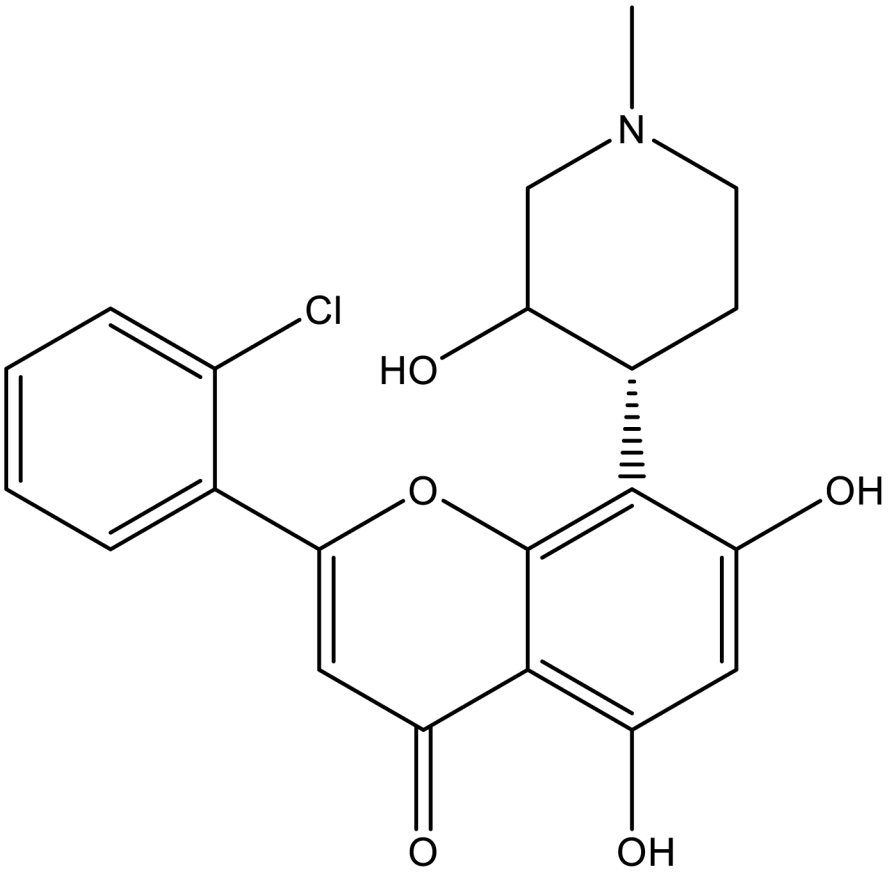
Flavopiridol is a synthetic flavones that blocks ATP binding by competing with its substrate and directly inhibits the kinase activity of multiple CDKs that are essential for the transition of the cells from the G1 phase to the S phase (G1/S) or from the G2 phase to the M phase (G2/M) of the cell cycle. It specifically inhibits CDK1, CDK2, CDK4, CDK6, and CDK7 which in turn prevents the phosphorylation of other proteins needed for the activation of the other CDKs. This leads to significant changes in the synthesis of mRNAs that encode for cell growth and apoptosis regulators, which subsequently restores the cell cycle control by controlling the uncontrolled proliferation of the tumor cells. Due to this mechanism of action, flavopiridol is often referred to as a pan-CDK inhibitor.

Moreover, several phase I trials are underway to exploit the synergistic relationship between flavopiridol and taxanes like paclitaxel. The administration of flavopiridol after taxanes is the preferred sequence in this relationship as cell death by taxanes occurs only when the cells exit the abnormal mitosis. This exit is facilitated by a reduction in the CDK1 activity which can be achieved by the use of flavopiridol, and therefore hastens apoptosis (Shapiro, 2004).

Another promising congener of rohitukine is P-276-00 which is also classified as a novel small molecule inhibitor of CDKs. This molecule shows high selectivity to CDK1-B (CDK1 coupled with cyclin B), CDK4-D1 (CDK4 with cyclin D1), and CDK9-T1 (CDK9 in association with cyclin T1) when compared to CDK2-E (CDK2 couple with cyclin E) and CDK7-H (CDK7 with cyclin H).

By depleting the levels of cyclin D1 and CDK4, this molecule was found to restore the unchecked cell growth in human non-small cell lung cancer and human breast cancer cell lines. In addition to these effects, P-276-00 is also capable of up-regulating caspase-3 activity and activating apoptotic events in

Figure 12. Structure of flavopiridol



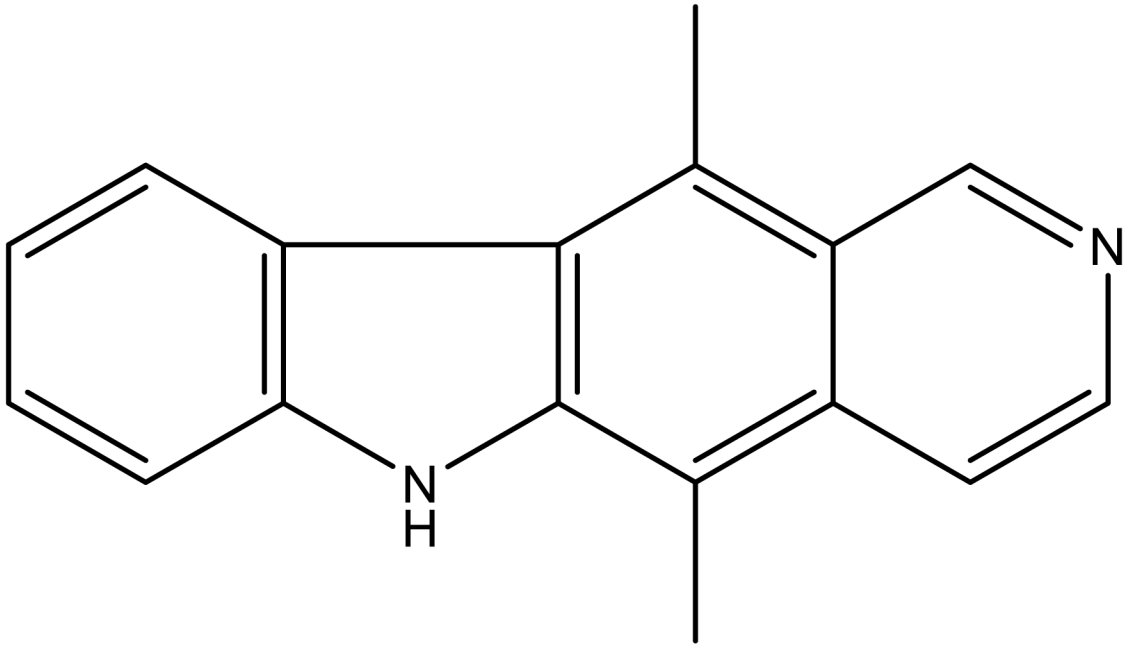
tumor cells. This congener has potent anti-neoplastic activity in both chemo-sensitive and chemo-resistant cancer cell lines. As of late, this molecule is undergoing phase II trials for it cytotoxic efficacy in an advanced form of refractory neoplasm, multiple myeloma, and mantle cell lymphoma (Shirsath et al., 2012).

7. Ellipticine

Ellipticine is a naturally occurring alkaloid that is prevalent in a large number of Apocyanaceae plants and possesses significant anti-cancer activity. Several derivatives of ellipticine have been generated by manipulating the planar tetracyclic structure of this molecule and these have been exploited for antitumor response in cell lines. The alkaloid and its derivatives exert anti-cancer activity by diverse mechanisms. Ellipticine mainly acts by intercalating with the DNA and inhibiting the activity of DNA Topoisomerase-II (Top II).

Furthermore, it alters the stability and the assembly of the pre-initiation complexes by targeting the interaction between the ribosomal RNA (rRNA) promoter and the SL1 (a promotion recognition essential transcription factor). It also interacts with the telomeric DNA region to inhibit the telomerase activity and causes damage to the DNA by forming covalent DNA adducts post activation by cytochrome P450.

Figure 13. Structure of ellipticine



In addition to the DNA damaging mechanisms, ellipticine also shows considerable activation of the p53 tumor suppressor protein to induce cell-cycle arrest (Miller et al., 2019).

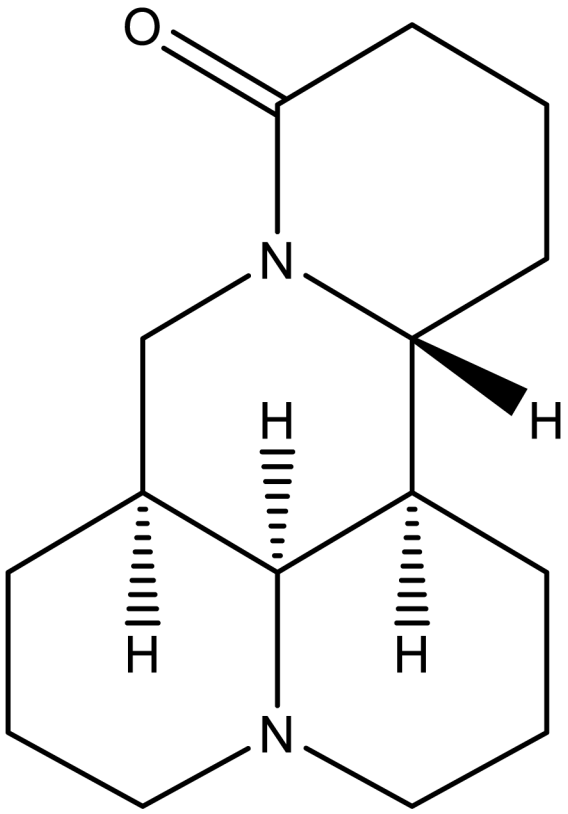
Recently, it was discovered that this alkaloid could also inhibit c-kit, a kinase associated with highly malignant cancers. The c-kit involved in this pathway is a stem cell factor receptor which plays a vital role in cell differentiation, maturation, and functioning. Binding of the stem cell factor to the c-kit receptor initiates auto-phosphorylation that, in turn, leads to the activation and downstream signaling of other kinases and activators involved in cell growth and apoptosis. Mutations in this receptor is correlated with the uncontrolled cell proliferation and ellipticine keeps this in check by blocking the mutant c-kit (Thompson et al., 2008).

a. Toxicity profile:

Some derivatives of this alkaloid like celiptium and 9–hydroxyellipticine (9HE) have been validated for use in clinical trials but these have been discontinued at the stage II owing to their adverse effects. This includes nausea, vomiting, muscle cramps, fatigue, pronounced mycosis of the tongue and esophagus, as well as mouth dryness. Other toxic effects that were frequently reported were intravascular hemolysis, xerostomia, and azotemia.

9HE has a higher affinity for DNA intercalation when compared to the parent compound, ellipticine. This derivative induces cell death by decreasing p53 phosphorylation and blocking the cell cycle at the G0/G1 phase (Andrews et al., 2013). Albeit its drawbacks, ellipticine and its derivatives have opened a window of opportunities in anti-cancer therapeutics by putting forth a diverse set of molecular targets.

Figure 14. Structure of matrine



8. Matrine

Matrine is a tetracyclo-quinolizidine alkaloid obtained from the roots of the Chinese therapeutic herb, *Sophora flavescens Aiton*. This molecule has been studied for decades on account of its pharmacological uses as an anti-inflammatory, immuno-modulatory, anti-pyretic, and anti-hepatitis B antiviral agent among others.

However, the main therapeutic use of this alkaloid for which both the parent compound and its derivatives have been extensively studied is its anti-neoplastic activity. This plant has been widely used in China as a part of the traditional Chinese medicine Kushen injection which is the dried root of *S.flavescens* containing matrine, oxymatrine, and other products (Zhang et al., 2020).

This injection is used as an adjuvant therapy in the treatment of lung cancer, breast cancer, pancreatic cancer, colon cancer, gastric cancer, liver cancer, esophageal cancer, glioma cancer, cervical cancer, and to relieve cancer-related pain. Matrine has also been approved by the Chinese State Food and Drug Administration (SFDA) for its use as an anti-cancer agent.

Matrine induces antitumor activity by inhibiting the cancer cell proliferation, inducing apoptosis, and preventing the metastasis of these cells. Additionally, it is also found to reverse the drug resistance

developed by the tumor cells and lower the toxic effects that manifest with the use of other anti-cancer agents (Rashid et al., 2019).

a. Mechanism of Anti-Cancer Action in Different Tumor Cells

The anti-cancer mechanism of matrine is distinct for each type of cancer and this is discussed below. In lung cancer, matrine blocks the cell cycle at the G1/G0 phase and increases the expression of the microRNA (miR)–126. It then down-regulates or lowers the levels of the vascular endothelial growth factor (VEGF) which targets the miR–126 and finally results in apoptosis (An et al., 2016). Moreover, it also up-regulated the levels of p53 and p21 with a simultaneous reduction in the levels of proliferating cell nuclear antigen to prevent both tumor cell proliferation and migration (Z. Lu et al., 2017).

Other studies had also discovered that matrine elicits its activity by activating the p38 pathway and other signaling pathways. Inhibition of the inhibitory κ B kinase β (IKKβ), a key regulator of the NF-κB signaling pathway, and down-regulation of hexokinase II are the main ways in which matrines inhibits the proliferation of breast cancer cells. In hepatic carcinoma, this alkaloid acts by inducing mitochondrial dysfunction and generating oxidative stress that in turn promotes endogenous apoptosis.

A similar mechanism involving the generation of reactive oxygen species occurs when matrine is used to treat gallbladder carcinoma and pancreatic cancer (Minna Huang & Xin, 2018). The induction of protective autophagy through extracellular signal – regulated kinase (ERK) pathway, and the inhibition of the migration as well as proliferation of the osteosarcoma cells by the ERK/NF-κB pathway is yet another mechanism of action of matrines (Ma et al., 2016). Besides this, it is also found to induce cell senescence and down-regulate the levels of proteins such as insulin – like growth factor to effectively inhibit the growth of multiforme glioblastoma (W. Zhou et al., 2018).

Apart from its anti-cancer effects, the reversal of drug resistance of cancer cells to other anti-neoplastic agents is also seen with the use of matrine. Lung cancer cells that have developed resistance to cisplatin can be re-sensitized by the regulation of the β–catenin/ survivin signaling pathway by matrines. On top of this, a combination of matrine and cisplatin in the ratio of 2,000:1 is found to be capable of synergistically inhibiting the proliferation and invasion of urothelial bladder cancer cells by promoting apoptosis (X.-Z. Liao et al., 2017).

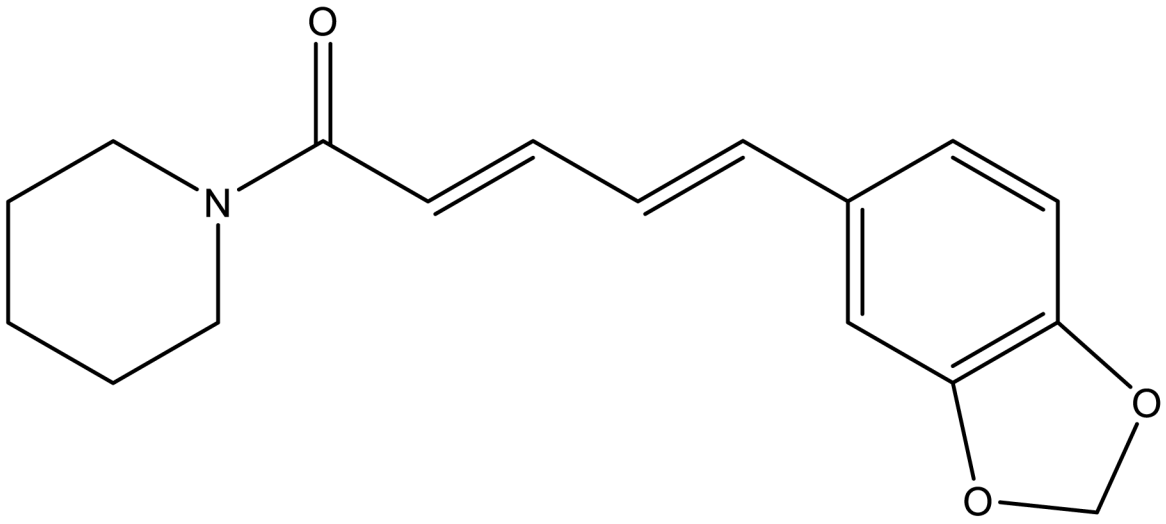
9. Piperine

Black pepper or *Piper nigrum* is a common household spice that has been widely used for both culinary and medicinal purposes. The fruits and seeds of this medicinal plant have immense therapeutic potential due to which it has been widely used as a folk medicine. Despite being a potent anti–inflammatory, immune-modulatory, anti-oxidant, and anti-ulcer agent, this plant is well known for its anti–cancer activity.

Black pepper generally does not cause any significant side effect when taken in small quantities, However, large quantities have been reported to cause some side effects like loss of potassium, acid reflux, nausea, constipation, allergic reactions like hives, and even respiratory infections in some cases.

The pharmacological activities elicited by this plant are often attributed to the presence of an active pungent constituent called piperine. This alkaloid elicits anti-cancer effect by promoting apoptosis and arresting the cell cycle at different stages by influencing the checkpoints and regulator proteins (Turrini et al., 2020).

Figure 15. Structure of piperine



a. Mechanism of action

In breast cancer cells, this compound was found to activate caspase 3, trigger the cleavage of several key cellular proteins which led to apoptosis, and arrested the cell cycle at the G2/M phase by mitigating the expression of cyclin B1. Piperine also acts as an effective inhibitor of prostate cancer cells by attenuating the expression of the transcription factor, STAT 3 (signal transducer and activator of transcription 3) and NF–κB (Samykutty et al., 2013). In osteosarcoma cells, this alkaloid down-regulated the expression of cyclin B1 and enhanced the activation of CDK1 and checkpoint kinase 2 (Chk2) which in turn halted the cell cycle at the G2/M phase.

Melanoma cells and human rectal adenocarcinoma cells have also been receptive to the anti-proliferative activity induced by piperine. In these cells, piperine induces apoptosis by the generation of reactive oxygen species (ROS). It is also found to arrest the cell cycle at the G1 phase in the colon carcinoma cells by down-regulating the expression of CDK4–D1 and CDK6–D3, preventing the phosphorylation and subsequent activation of retinoblastoma protein (pRb), and inducing the release of CDK inhibitors, p21 and p27 (Yaffe et al., 2015).

An anti-apoptotic protein that is highly expressed in the tumor cells is survivin. This protein is involved in the regulation of cytokinesis as well as the progression of cell cycle and is expressed as a result of the cellular events taking place during the AkT signaling. The pro–apoptotic effect of piperine is closely connected with the levels of survivin.

In colon cancer cells, piperine inhibited not just survivin but also the activation of its transcription factor p65 and induced the activation of procaspase-3 and -7 (zymogen precursors of caspase 3 and 7) which ultimately resulted in the apoptosis of the cancer cells (Rather & Bhagat, 2018).

Multi-domain proteins called matric metalloproteinases (MMP) have a dual role in cancer progression. They promote the growth of the tumor cells and enhance cancer-associated angiogenesis. MMP-1,

MMP-3, MMP-9, and MMP-13 have been identified to play a role in the growth and invasiveness of breast cancer cells.

Piperine plays a significant role in preventing breast cancer metastasis as it lowers the expression of MMP–9 and MMP–13 (Merdad et al., 2014). This effect is brought about by the inhibition of two signaling networks namely, protein kinase C–α mediated activation of ERK 1/2 signaling and NF-κB dependent activation of activator protein–1 (AP–1). In addition to these effects, piperine has also demonstrated considerable activity in inhibiting cancer stem cells (CSCs), especially in breast cancer. It alters the breast CSCs self–renewal properties by inhibiting the Wnt/β–catenin signaling pathway, a fundamental signaling network involved in the self–renewal and differentiation of CSCs (Kim et al., 2012).

Another notable anti-cancer mechanism of action of piperine is its ability to stabilize the G–quadruplex DNA structures. These non–canonical DNA structures are generated in the regulatory regions of the oncogenes when the G–quartets undergo square planar arrangements during DNA metabolism. These structures lead to genome instability and promote cancer development by regulating key cellular processes like replication, transcription, and translation.

Interestingly, it has been discovered that piperine bound to the G–quadruplex structures at the c–Myc promotor region with a high affinity. This binding has led to the stabilization of the G–quadruplex structures which, in turn, down-regulated the expression of the c–Myc oncogene in cancer cells (Tawani et al., 2016).

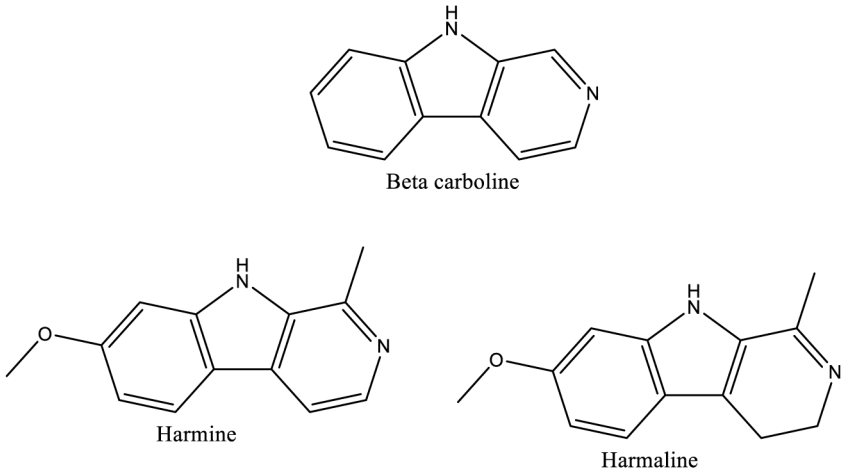
10. β – Carboline Alkaloids

Carbolines are a group of naturally occurring alkaloids in which the indole ring is fused to the six–membered pyridine ring. Based on the position of the nitrogen in the pyridine ring, this group is classified into four types namely, α–carbolines, β–carbolines, ϒ–carbolines, and δ–carbolines. Among these, β–carbolines remains to be the most extensively investigated group owing to its pharmacological activities. This group of alkaloids have been isolated from a plant called *Peganum harmala* and has been widely employed for the treatment of malaria and alimentary tract cancers (Lakshmi Manasa K, Swetha Yadav S, Srikanth D, 2020).

Harmine, harmane, harmaline, norharmane, and tryptoline are some of the best known β–carbolines. Structure activity relationships have shown that the antitumor activity of this group is attributed to the presence of the β–carboline scaffold which is a planar tricyclic system. Substitution of the 1st and 3rd position of the basic nucleus with either a phenyl or a heterocyclic group has shown potent antitumor activity. In contrast, the substitution of the nitrogen at the 9th position of the scaffold with a methyl or benzyl group led to increased affinity with the DNA.

Additionally, it has also been uncovered that dimerization of two β–carbolines with a suitable linker group led to a significant improvement in the binding of the molecule with the DNA. On top of this, studies have also revealed that substituting the 9th position with n – butyl or phenylpropyl led to the development of pharmacophores with enhanced antitumor activity. Incorporation of an amino group at the 1st position or addition of a flexible amino side chain at the 3rd position of the β–carboline nucleus has also been associated with an increased cytotoxic effect as this increased the affinity between the alkaloid and DNA (Gu et al., 2018).

Figure 16. Structure of β–carbolines



a. Structure activity analysis

Several β–carboline derivatives have also been designed using strategic manipulation of the basic scaffold at the 1st, 3rd, and/or 9th position in many cases. For instance, 9–substituted norhormane demonstrated enhanced DNA–intercalating ability, inhibition of DNA topoisomerase as well as CDK of the cancer cell lines, HeLa and BGC–823. A similar observation was made when this position was incorporated with a disubstituted aryl group and tested with human leukemia cells (HL–60) as this led to the growth inhibition of the HL–60 cells.

Norhormane–Ruthenium–II complex and its derivative tris–chelate polypyridyl also demonstrated significant anti-cancer activity by activating caspase–9 and caspase 3/7 which, in turn, initiated a series of cellular events that induced apoptosis by the p53 signaling network. Conjugation of norhormane with salicylamide is also associated with better control of liver and colon cancer cells.

In the liver cancer cells, this conjugated molecule led to apoptosis by increasing the expression of the pro–apoptotic protein, Bax and causing mitochondrial membrane depolarization (Sahoo et al., 2019). This mode of action is not just restricted to the derivatives but also to parent compounds like harmine and other β–carbolines. Dimerization of the β–carbolines with simultaneous incorporation of a methyl or benzyl substituent at the 9th position elicited antitumor activity by arresting the cell cycle at the S and G2/M phase. These derivatives also induced apoptosis in a dose–dependent manner by down-regulating the expression of the protein, cytochrome–C and bcl–2 protein (Z. Chen et al., 2011).

b. Mechanism of action

β–carboline alkaloids act as anti-cancer agents by two main mechanisms, namely DNA intercalation and inhibition of DNA Top I and Top II enzymes. These topoisomerase enzymes are essential for a number of critical DNA processes such as replication, recombination, transcription, condensation of chromosomes during cell cycle, and also for maintaining the stability of the genome. Comprehensively

studied β–carbolines like harmine, harmane, and harmaline demonstrated an inhibitory effect on the Top I by DNA intercalation.

These agents elicited this action by binding to either the minor groove of the DNA or to the cleavable DNA–topoisomerase complex. This ability was imputable to the presence of the planar ring system in these alkaloids and this is evinced by the fact that harmaline which lacked this ring showed a less potent cytotoxic effect in contrast to the other two agents. Cell cycle arrest by harmine is brought about by the inhibiting the phosphorylation of pRb which is responsible for inactivating this tumor suppressor protein.

Moreover, it also down-regulates the levels of vital cell cycle regulating kinases including CDK2, cyclin A and cyclin B1. Harmine is also capable of inducing DNA damage and preventing DNA repair by reducing the expression of Poly (ADP–ribose) polymerase–1 (Parp–1) enzyme (Mota S.R.S. et al., 2020).

11. Other Alkaloids

Tabernaemontana catharinensis, a plant belonging to the genus *Tabernaemontana* is extensively used as an anti-cancer remedy by the natives of Brazil, Paraguay, Argentina, and Bolivia. The antitumor activity of this plant is attributed to the presence of three indole alkaloids, namely coronaridine, heyneanine, and voacangine. These alkaloids are extracted from the root bark of the plant and have been proven to induce apoptosis in human laryngeal carcinoma (Hep-2) cells.

Coronaridine is more potent than the other indole alkaloids obtained from this plant as it also damages the DNA of the tumor cells. This alkaloid, however, is non-specific in its action as it affects even the normal healthy cells (Mondal et al., 2019). Another novel anti-cancer alkaloid that has recently been isolated from the roots of *Melodinus khasianus* is khasuanine A. This compound induces apoptosis by the activation of caspase 3 and tumor suppressor protein p53with simultaneous inhibition of the cell death regulator protein, Bcl-2 (J. Zhou et al., 2017).

Another compound with great potential as an anti-neoplastic agent is cryptolepine, a major indoquinoline alkaloid derived from the African anti–malarial plant, *Cryptolepis sanguinolenta*. It acts by inhibiting Top II enzyme and causing DNA damage by the p53–mediated signaling networks. Cryptolepine causes DNA intercalation especially at the CG (Cytosine-Guanine) rich sites and in the non–alternating CC (cytosine–cytosine) regions, and perturbs the cell cycle at the G1 phase. In addition to this, it promotes apoptotic cell death by inhibiting the proto-oncogene Bcl–2, inducing the release of the cyt C in the cytosol, and activation of caspase–3 (Ansah & Mensah, 2013).

Sanguinarine is a benzophenanthridine alkaloid that has proven anti-cancer effects in human squamous cell carcinoma cells, human prostate cancer cells, and pancreatic carcinoma cells. In human pancreatic cancer cells, it up-regulates the expression of pro–apoptotic proteins (Bax, Bak, and Bad) and down-regulates the expression of anti–apoptotic proteins (Bcl–X_L and Bcl–2). The deregulation of these proteins lead to the apoptosis of the cancer cells (Ahsan et al., 2007).

In addition to this, it has been postulated that sanguinarine could have the potential to positively influence the mutations in the p53 protein that is interlinked with the development of chemotherapy–and radiation–resistant tumor cells. This reasoning behind this is the fact that the alkaloid decreases the levels of mutant p53 and stimulating its phosphorylation, especially at the serine–15 residue in the pancreatic cancer cells. This is believed to restore the wild–type function to the mutant p53, although further studies are still required to properly establish this (Dong et al., 2003).

Moreover, sanguinarine has also been identified to have potent inhibitory effects on the growth of malignant glioma cells by the generation of ROS and activation of the ERK 1/2 signaling pathway. This

subsequently resulted in both apoptosis and autophagy of the glioma cells. Apoptosis was achieved by the decreased expression of procaspase–8, -9, and –3, while autophagy was mainly regulated by the increased expression of Atg 5 and Beclin–1 (autophagy related proteins) (Pallichankandy et al., 2015).

A novel anti-cancer alkaloid which has shown considerable inhibitory activity against several tumor cell lines and even multi–drug resistance breast cancer cells is evodiamine. This bioactive compound is extracted from the medicinal plant *Evodia rutaecarpa* and induces apoptosis by activating caspase–dependent pathways in human melanoma cells, acute leukemia cells, and in androgen–dependent as well as androgen–independent cancer cells (Jiang & Hu, 2009). Translocation of the apoptosis inducing factor into the nucleus is also brought about by this alkaloid.

Furthermore, it is also capable of arresting the cell cycle at G2/M transition and resulting in apoptotic cell death by phosphorylation of the Raf–1 enzyme at its serine residue. In addition to this, this novel alkaloid is also found to promote the formation of microtubule bundles and increase microtubule polymerization in multi–drug resistant breast cancer cells. In this manner, evodiamine is shown to elicit a greater antitumor activity against these cells at a lower dose when compared to that produced by paclitaxel (C.-H. Liao et al., 2005). These clearly define the potential of evodiamine as a highly promising anti-neoplastic agent but additional studies are needed to further understand the mechanism behind this.

CONCLUSION

Several natural products have been extensively screened for their anti-cancer activity, but only a few potent bioactive constituents have developed as chemotherapeutic agents. The advancement in modern technologies and biotechnological methods has led to the laborious task of isolating and purifying these agents from natural sources. Bioassay-guided isolation techniques have shown significant success in characterizing newer anti-cancer agents, but this basic procedure is a time-consuming process. Development in molecular biology, together with more sensitive and rapid analytical techniques, will increase the efficiency of testing these products on a large scale (Shoemaker, 2006).

Bioinformatics strategies can also be applied to screen large databases of natural products saving both time and cost while detecting natural anti-cancer drug candidates. Humans have been using natural compounds derived from animals, plants, and microbes since prehistory. The treatment of cancer, in particular, has undergone a revolution owing to the recent progress in genomics. Although many therapeutics of natural origin have been applied to treat cancer, they are yet to advance to drug development stages due to limitations of solubility and cytotoxicity.

Devising alternative methods to get a workable supply of these molecules must be exploited to satisfy commercial needs. Popular anti-cancer agents such as vinca alkaloids, paclitaxel, and camptothecin have been extracted from natural sources. Many more promising alkaloids remain unexplored, and these, when discovered, could change the outlook of cancer treatment in the 21st century. Undoubtedly, the fields of cancer drug discovery and natural products are amid substantial change as the latter is bound to bring newer dimensions to the former (Harvey et al., 2010).

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Chapter 17
Lectin as an Anticancer Therapeutic Agent

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ABSTRACT

Every year nearly 9.6 million people die from cancer worldwide. One third of cancer deaths are due to behavioural and dietary risks and lack of physical activity. Lectins are powerful oral and parental immunogens and some of their physiological effects are intricately linked to interference with immune function. Lectins are produced by wide range of living organisms from microbes to mammals. They function as both allergens and heamagglutinins. Various lectins have been identified which are associated with different types of cancers. Because of this property, they are currently employed as therapeutic agents in cancer treatment.

1. INTRODUCTION

Cancer is one of the most deadly diseases of the 21st century and will remain at a high peak in the future. Cancer is a disease in which the cells divide uncontrollably and can invade in nearby tissues. In normal situations, when the body requires, the cells grow and divide. When the cells become older or get damaged, they undergo programmed cell death (PCD) or apoptosis and the old cells are replaced with the new ones. This tidy process is distressed when new cells are formed when they are not needed and the

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aged cells do not die when they should die. These extra cells lump together to form a tumor (Gupta et al., 2011). DNA is found in every single cell in the body and controls all its activities. Cancer is instigated by damage to the DNA replication mechanism. The normal healthy cell is able to repair damaged DNA but is unable to do so in cancer cells and harm the cell when injured or damaged cells undergo uncontrollable cell division. They form lumps or masses of tissues called tumors. Tumors can be malignant or benign (Dhillon et al., 2011, Ferlay et al., 2014). In a malignant tumor, mutation and expansion lead to tumor growth and progression, ultimately it can break off the basal membrane barrier surrounding the tissues and spread to other regions of the body. The spread of cancer from one part of the body to another part is called metastasis (Klein, 2008). Benign tumors are not cancerous and can often be removed in most of the cases. Cells in benign tumors do not spread to other regions of the body.

1.1 What causes cancer?

The main cause of cancer is the transformation of normal cells that usually progress from a pre-cancerous cell to a malignant tumor in a multistage process. A person's genetic factors and environmental factors are responsible for this conversion. In the environment, various carcinogens are present which are responsible for the development of cancer which includes:

- Physical carcinogens, such as non-ionizing and ionizing radiation
- Chemical carcinogens such as cadmium, nickel, benzene, vinyl chloride, asbestos, aflatoxin (a food contaminant) and arsenic
- Biological carcinogens such as viruses, harmful bacteria and a few parasites

It has been observed that the incidences of cancer increase with age. Examples of age-specific cancer are stomach, colorectal and pancreatic cancer. As a person gets older, cellular repair mechanisms become be less effective thereby increasing the risk of cancer.

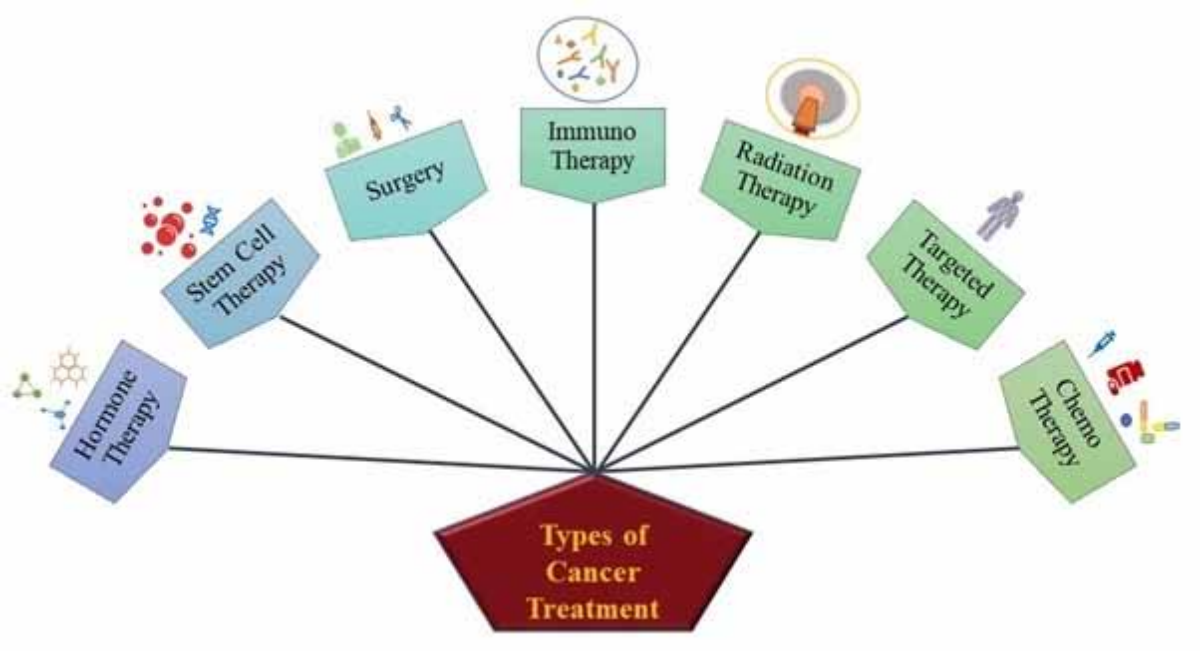
1.2 Treatment

Significant efforts are being made by researchers for the identification of new cancer therapeutic agents from marine sources, plants sources, synthetic sources. The development of new formulations to enhance the therapeutic effects of existing anticancer agents with minimal side effects are also being studied.

In modern times, generally accepted treatment of cancer is surgery, cryosurgery, electrosurgery, bone marrow transplantation, hormone therapy, radiotherapy and chemotherapy (Fig. 1). Nowadays, various immune therapies and smart drug delivery systems, targeted drug delivery are also used for cancer treatment. Treatment of cancer depends upon the type of cancer, location of the tumor, assertiveness, phase of the disease and, the patient's overall condition as well as illness of the patient. Treatment of cancer is a combination of surgery with chemotherapy and radiotherapy, or alone (Madhu et al., 2019).

Several therapies like hormone therapy, stem cell, surgery, immune therapy, radiation, chemo and targeted therapy are being used for the treatment of various types of cancer.

Figure 1. Cancer treatment therapies
(Source: *https://positivebioscience.com/types-of-cancer-treatment/***)**



1.3 Modern medicine

Modern medicine is a quick way of curing a diseased condition. Modern medicine is beneficial in that it is precise and fast when used to address a particular disease. The disadvantage of modern medicine is that most of the drugs used are toxic to the body or tissue hence it is recommended only for life-threatening, deadly or incurable diseases. Also, it is easy for microbes to adapt and become resistant to these modern drugs. Thus, the use of herbal medicine is encouraging in certain medical conditions to bring the body back to normal allowing it to fight diseases on its own, thus eliminating resistance. Around the world, about half a million medicinal plants provide promising futures as most of them are not investigated yet for their active principles and their hidden potential in the treatment of present and future studies.

In this context, it is essential to screen medicinal plants for the presence of different proteins such as lectins, proteases, or protease inhibitors which possess interesting properties and clinical applications. Lectins are of non-immunogenic carbohydrate binding proteins that agglutinate cells, glycoconjugates, show a specific, noncovalent binding activity to carbohydrates and sugar-containing substances whether free in solution or on cell surfaces without changing covalent structure of any glycosyl ligand (Beuth et al., 1995).

2. BACKGROUND

Lectins from plant sources were reported in the year 1888 and were discovered by H. Stillmark, a Russian Scientist, who investigated the toxic compound from the crude extract of castor bean seed because

of their ability to agglutinate red blood cells and hence they were called Phytohemagglutinins (Sharon, 2004). They were renamed as "lectins," a term deduced from the Latin word "Legere," meaning "to select.". Because this agglutinating activity could be inhibited by simple carbohydrates, it was clear that carbohydrate residues on cell surfaces, extracellular matrix, and excreted glycoproteins were the targets of the lectins. These lectins particularly bind sugar moieties of the glycoprotein which furnish the surface of most of the animal cells.

Therefore, lectins can be defined as non-immunogenic specific binding proteins of carbohydrates that agglutinate cells, glycoconjugates, show reversible noncovalent binding activity to carbohydrates and sugar-containing substances whether free in solution or on cell surfaces without changing covalent structure of any glycosyl ligand. Due to their unique carbohydrate specificity, various plant lectins are utilized for many applications including cancer therapy and virus research. Many modifications in sugar structure are seen in cancer cells, compared to normal cells like excessive sialylation, fucosylation and branching of complex sugar or random appearance of some new structures, termed as aberrant glycosylation (Lei-lei et al., 2011). In this regard, lectins are exceptional tools in cancer research and therapy because of their efficacy in the identification of the changes that occur in cancerous cells, for decreasing the cell tumorigenicity and also metastasis and angiogenesis (Estrada-Martínez et al., 2017).

3. LECTINS AS CANCER BIOMARKER

Since last twenty years, researchers are working on specific lectins which can differentiate cancerous cells and non-cancerous cells by means of lectin glycan interactions (Wu et al., 2012). Interestingly, the majority of cancer biomarkers that are currently being used in clinical settings are lectins, which are structurally altered in their glycan moieties and aberrantly expressed (Henry & Hayes, 2012). Cancer Antigen 15-3 (CA15-3) and alpha-fetoprotein (AFP) are clinically monitored in the therapy for glycan changes for hepatocellular carcinoma and breast cancer. The other cancer biomarkers are being monitored for their total protein levels (Kuzmanov et al., 2013). It is believed that glycosylation changes are involved in oncogenic transformation as glycans are responsible for cancer developing processes, such as cell signaling, angiogenesis, cell-matrix interactions, immune modulation, tumor cell dissociation, and metastasis. Glycosylation changes that are commonly associated with cancer transformation include sialylation, fucosylation, increased GlcNAc-branching of N-glycans, and overexpression of truncated mucin-type O-glycans (Pinho & Reis, 2015).

The applications of lectins in cancer biomarker discovery include immobilized lectin affinity chromatography, enzyme-linked lectin assay, lectin histochemistry, lectin blotting and lectin array. A brief overview of these techniques is described below.

3.1.1 Immobilized-Lectin Affinity Action

Immobilized-lectin affinity action could be a technique for separation of compound proteins supported by extraordinarily specific interaction between a glycoprotein, that's immobilized onto a specific matrix, and its carbohydrates ligands (Hage et al., 2012) (Fig. 2). Once complemented with spectrometry analysis,

this technique helps in analysis to verify potential cancer biomarkers. This can be the foremost effective technique utilized in cancer biomarker analysis for the enrichment of glycoproteins.

3.1.2 Enzyme-Linked Lectin Assay

Enzyme-linked glycoprotein assay could be a technique that adopts the principle of enzyme-linked immunosorbent assay but uses glycoprotein together with the reagents instead of antibodies. McCoy et. al. (1983) introduced this system within the early eighties. In a direct assay, samples that contain glycoconjugate are coated directly onto the wells of a microtiter plate, followed by the addition of associate enzyme-linked lectin, which is ready to then bind to their glycan structures (McCoy et al., 1983). A colored product is produced from the substrate by an enzyme whose intensity is used to estimate the coated glycoconjugates levels by a photometer. Specific lectins are chosen rigorously counting on the glycan structure that must be detected. This assay needs minimum time and is simple to perform. One disadvantage of this assay is that lectin must always include proteomic analysis or protein detection for its identification. The method is illustrated in figure 3.

A glycoprotein of interest is conjugated with the gel matrix in a column through which the body fluid of the cancer patients is passed in order to check for the presence of potential biomarker. Upon washing with the buffer solution, the non-bound glycoproteins get eluted while the column retains only the glycoprotein of interest which is eluted and identified by proteomics.

Here, three different methods are shown:

(A) In the direct assay, the microtiter plate coated with body fluid and then enzyme-conjugated lectin is added.

(B) In the hybrid assay, a microtiter plate is coated with antibody later enzyme-conjugated lectin is added to capture specific glycoproteins of interest

(C) In case of sandwich enzyme-linked lectin assay, two different lectins, first acts as capturing agent to which the desired glycoprotein will bind while the second one which is an enzyme-conjugated acts as detecting agent. The enzyme converts the substrate to a colored product which is detected to analyze the presence of glycoprotein.

3.1.3 Lectin histochemistry

Lectin histochemistry is similar to immunohistochemistry method by which cellular components that uses lectins instead of antibodies are visualized microscopically. Either direct or indirect labeling method can be employed in lectin histochemistry (Roth, 2011). On the basis of microscopy method, in the direct labeled technique, lectins can be directly bind to colloidal gold, fluorophores, enzymes or ferritin. Direct labeling method is less sensitive than the indirect method. However, the indirect technique employs use of enzyme linked-streptavidin or anti-digoxigenin respectively for the detection of biotin or digoxigenin conjugated lectin (Fig. 4).

According to Hashim et al. (2017), lectin histochemistry is widely used in the study of glycosylation changes in cancer tissues. In case of mucoepidermoid carcinoma tissues, the study demonstrated that the agglutinin, concanavalin A (ConA) could stain effectively all grades of the cancer tissues while staining with another lectin i.e. Ulex europaeus agglutinin (UEA-I) directly correlates with the degree of malignancy based on the intensity of staining. Muisuk et al. (2015) described the aberrant glycosylation of glycoconjugates in primary cholangiocarcinoma using multiple lectins. Cholangiocarcinoma is caused

Figure 2. Immobilized-lectin affinity process
(Redrawn after Hashim et al. 2017)

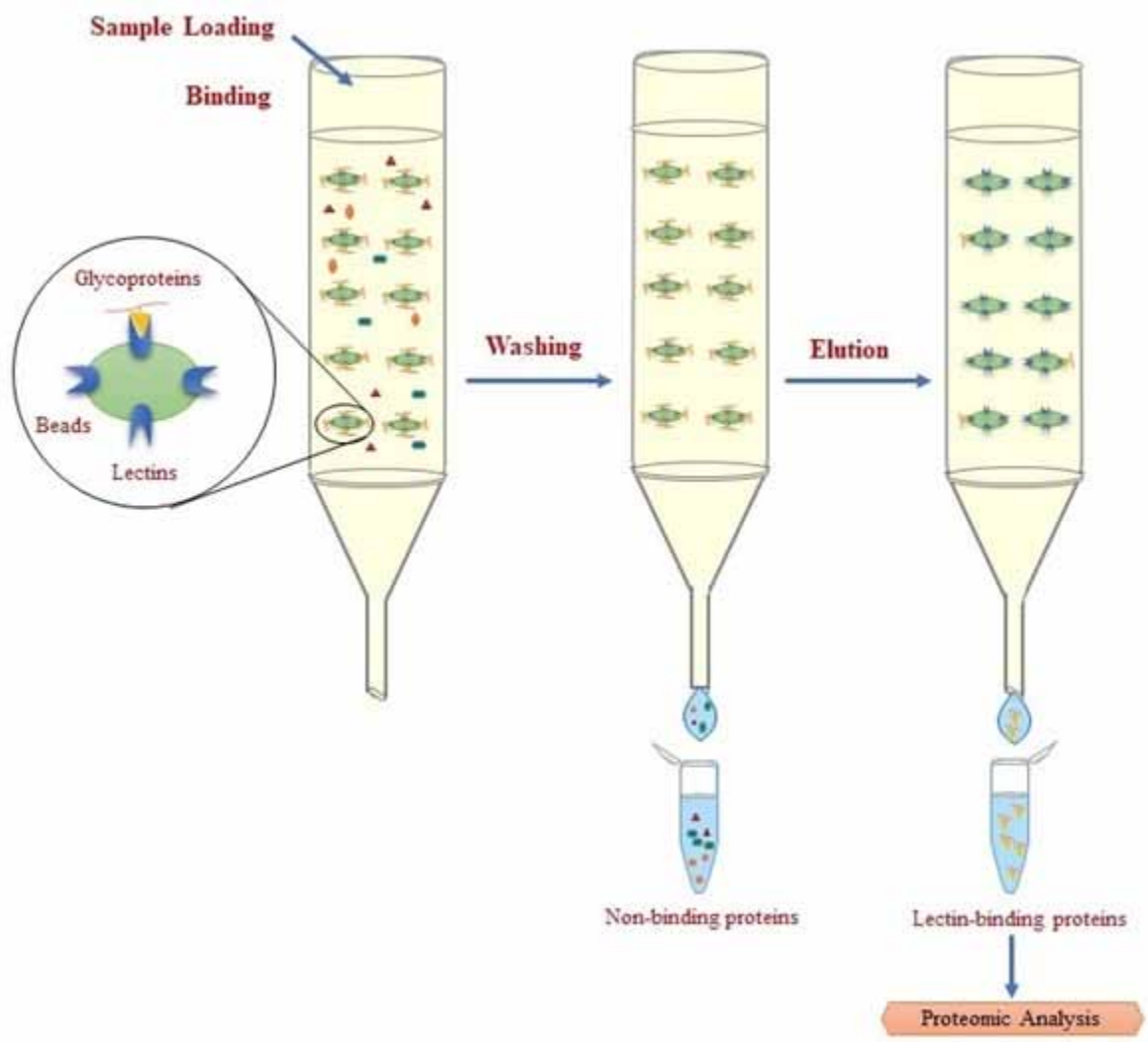


Figure 3. Enzyme-linked lectin assay approaches
(Redrawn after Hashim et al. 2017)

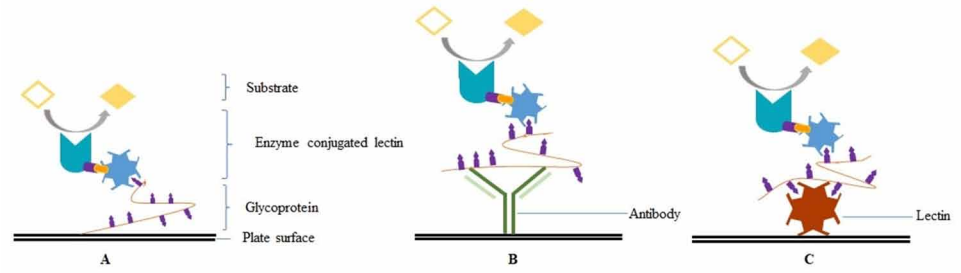
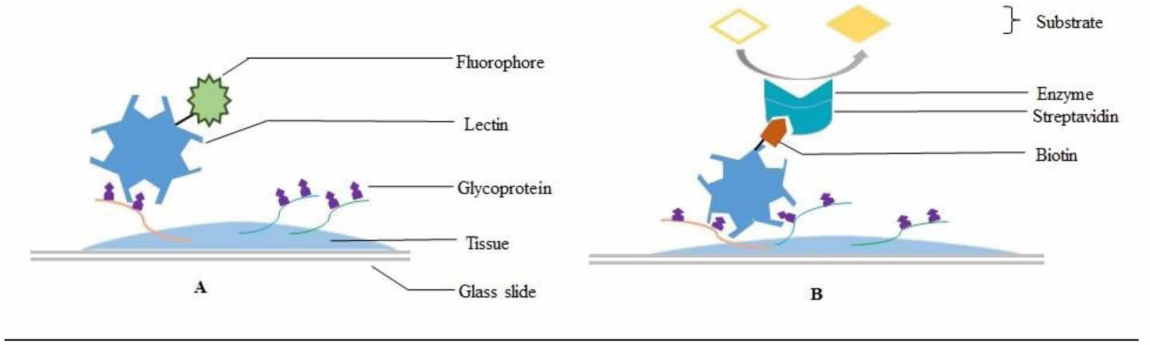


Figure 4. Lectin histochemistry technique
(Redrawn after Hashim et al. 2017)



by liver fluke infection usually seen in Thailand. Similarly, on the basis of various staining patterns, Sambucus Niagra Agglutinin (SNA) has showed promising findings in case of stage 0 breast cancer, ductal carcinoma *in situ* (Dos-Santos et al., 2014).

(A) In the direct technique, a fluorophore, enzymes, mixture gold or protein bound lectin is employed to detect glycoprotein of interest in a tissue sample which contains the glycoprotein. (B) In the indirect labeled technique, a hapten namely biotin or a digoxigenin is conjugated to a lectin, which are recognized by the enzyme linked-streptavidin or anti-digoxigenin complex respectively.

3.1.4 Lectin blotting

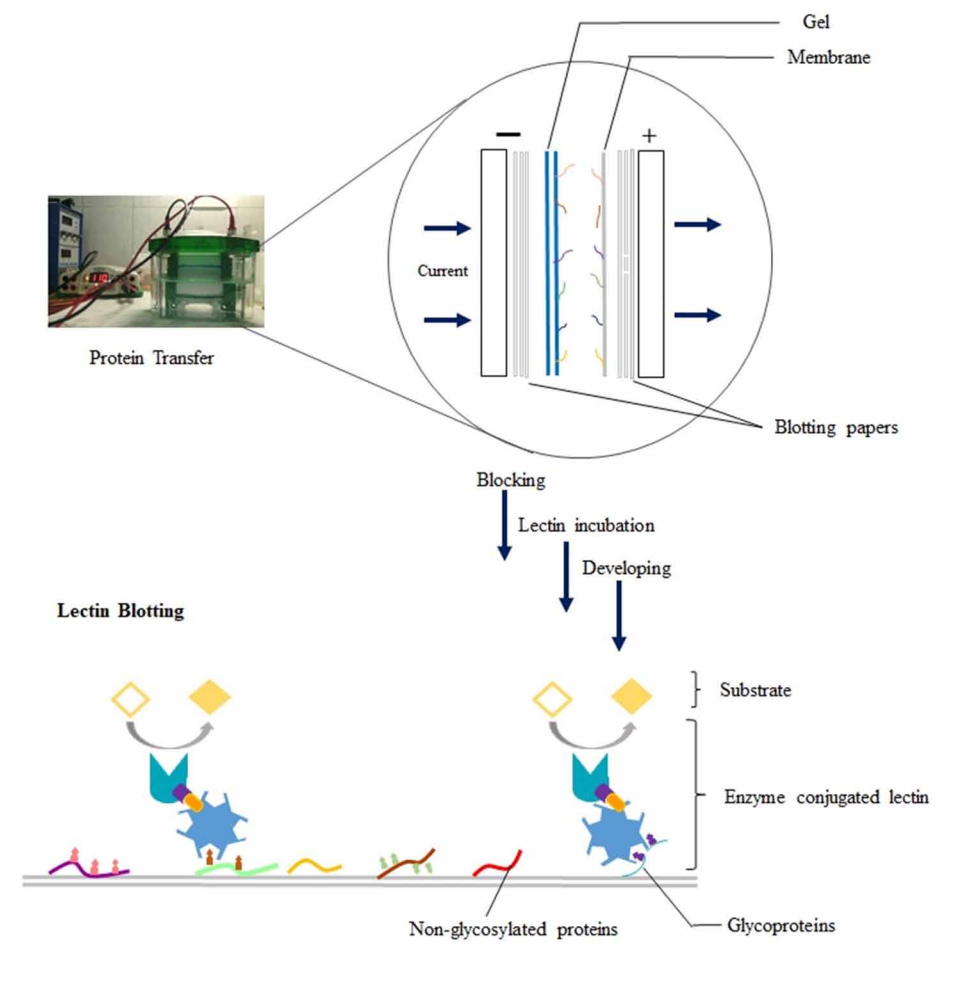
It is similar to western blotting where lectins are used instead of antibodies to detect glycoconjugates (Sharon, 2004). In this technique, polyacrylamide gel electrophoresis is performed to resolve the samples. A polyvinylidene fluoride (PVDF) or nitrocellulose membrane are then used to transfer the sample from the gel which is detected using glycan-specific lectin probes. In order to visualize the lectin complex, conjugates (for instance, enzymes, fluorescent dyes, biotin, digoxigenin, colloidal gold, and radioactive isotopes) are used. The concentration of lectin is crucial in this technique in order to lessen the false-positive binding. This technique is a powerful tool but not suitable for routine diagnostics (Fig. 5).

Similar to western blotting, in this technique, the proteins are transferred to a PVDF or nitrocellulose membrane after gel electrophoresis. The membrane is then subjected to obstruction associated incubation with lectins conjugated to a protein, biotin, digitoxin, mixture gold or hot isotopes which is then detected by the formation of colored product. Comparative analysis of cancerous verses non-cancerous samples will give information about aberrantly glycosylated proteins.

3.1.5 Lectin mircoarray

As the name suggests, the technique employs multiple lectins to detect the glycan making it rapid and sensitive technique. In a single experiment, many saccharide contents of glycolipids or glycoproteins can be detected by immobilizing the naturally derived lectins onto a solid surface. All those diseases in which glycoproteins are identified as biomarkers may be diagnosed with this assay, for instance Her2 (ErbB-2) in breast cancer, cancer antigen 125 (CA 125) in ovarian cancer and cancer antigen 19-9 in

Figure 5. Lectin blotting
(Redrawn after Hashim et al. 2017)



pancreatic cancer (Hu & Wong, 2009). Various researchers have used the method for the detection of a number of diseases. A glass slide is coated with glycoproteins or pre-treated with epoxides, N-hydroxyl succinimidyl esters, streptavidin and biotin (Hashim et al. 2017).

Study done by Shi et al. (2013) using pleural effusion from lung carcinoma to compare the glycoprotein from benign lung disease using lectin microarray identified unique glycoprotein profiles. Another study done by Li et al. (2018) among gastric cancer patients using serum samples by employing 50 tumor-associated-lectin microarray. They observed upregulation of GlcNAc, Tri/tetra-antennary N-glycan, GalNAc, α-linked fucose residues, β-1,6-GlcNAc branched structure and Tn antigen while down regulation of (α-1,3) Man residues and N-acetyl-D-galactosamine structure was observed. It is opined that GlcNAc may be an early prognostic biomarker for gastric cancer.

4. LECTIN AS A THERAPEUTIC TOOL FOR CANCER

Today plant lectins are widely used to inhibit pro-survival pathways (for instance, oncogenesis, Wnt signal, and super molecule synthesis) and particularly induce caspase-mediated cell death moreover as autophagy, by that cancer endure programmed cell death (PCD) (Ouyang et al., 2012; Ouyang et al., 2014; Lichtenstein & Rabinovich, 2013). However, precise mechanisms of that still unclear.

PCD Induced by Plant Glycoproteins

Direct organelle inactivation, sugar-containing receptors binding and endocytosis-dependent mitochondrial pathology are the three major pathways through which plant lectins can cause PCD.

The apoptosis inducing properties of Mistletoe and Ricin-B family lectins have been studied using cancer cells and found that they follow different pathways to cause this activity. They may bound to sugar containing receptors on cancer cell surface and trigger caspase medicate death pathway for instance, ConA and Polygonatum cyrtonema lectin (PCL) or follow the endocytosis dependent pathway and trigger autophagic necrosis such as in case of ConA.

i. Direct organelle inactivation

Mistletoe lectins (MLs) have been classified as type II ribosome activating proteins that have drawn a lot of attention attributable to their distinctive anti-cancer talents and medical care applications. There are two chains A chain and B Chain being carried by the members within the MLs taxon. The B chains once bind to sugar containing receptor of the outer cell membrane of cancer cell, it passes A chain into the cytoplasm. Later, the A chain inactivates the 28S ribosome synthesis thus inhibiting the protein synthesis.

ii. Endocytosis-Dependent Mitochondrial Pathology

Some plant lectins can internalized and bind to the mitochondria through clathrin-mediated endocytosis that binds to the mannose moiety of the glycoproteins present on the cellular membrane, for example, ConA (Ernst et al., 2003).

The internalized plant lectins are involved in the reduction of mitochondrial membrane potential (MMP) by targeting the cytochrome c leading to caspase-mediated cell death. Moreover, it also initiates the autophagy via the inductions of Bcl2/adenovirus E1B 19 kDa interacting super molecule three (BNIP3) (Chang et al., 2007, Hashim et al. 2017).

iii. Sugar-Containing Receptors Binding on the Cell Surface

In order to keep a check on the survival pathways, many plant lectins such as, Con A and PCL bind directly to sugar containing receptor present on the cell surface, signifying sugar-binding specificity can be one in all the most reasons motivating the anti-tumor activity (Xu et al., 2007; Gorelik et al., 2001).

All these three pathways are closely interlinked. The Ricin-B family lectins contain two chains A and B as mentioned earlier and bind to the cellular membrane receptors in order to inactivate the ribosome (Li et al., 2011). Con A, the foremost representative legume glycoprotein, might bind to matrix metalloproteinase family receptor triggers PCD through endocytosis and inhibit the tumor growth. The

endocytosis-dependent PCD is said to involve the receptors present on the mitochondrial outer membrane. As for the PCL of the *Galanthus nivalis* agglutinin (GNA) family, PCL-Fas binding would initiate caspase-dependent caspase-mediated cell death (Shi et al., 2013)

Pro-Apoptotic Pathway Activation and Inhibition of Anti-Apoptotic Pathway

The failure of the DNA damage repair mechanism initiates the apoptosis which acts as cellular defense and avoids cell proliferation. While studying the cancer cell models, it is found that the plant lectin triggers the pro-apoptotic pathway and keeps on checking the anti-apoptotic pathways (Shi et al., 2016). A number of ways are there by which plant lectin induces both apoptosis and autophagy in cancer cells by altering the signal transduction in molecular signalling pathways of PI3K/Akt, ERK, p53, Ras-Raf, ATG families, Bcl-2 family and caspase family. Cell shrinkage, nucleus condensation, DNA fragmentation, cell detachment. mitochondria membrane potential loss are few such signals that confirm the apoptosis process which can be examined by either using flow cytometry or microscopically or by performing specific assays for the detection of apoptosis (Yau et al. 2015).

The C-type lectins are crucial as it is involved in PCD, cell proliferation and immune response. The C-type superfamily comprised of selectins including L-selectin, P-selectin, and E-selectin, Natural killer-receptors (NK-receptors) and Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN). The perforin/granzyme pathway or Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and Fas ligand like death receptors are induced by NK cells for cancer suppression. DC-SIGN can induce enhance immuno-functioning in human colorectal carcinoma cells by binding to Le glycans which are expressed on these cells. The apoptotic properties of other C-type lectins are still under research (Yau et al. 2015).

The Mistletoe (Viscum Album) Lectin (ML-1) is most controversial with regard to cancer therapy. There are studies elaborating the pro-apoptotic effects of mistletoe lectin while there are others stating about its anti-apoptotic effects. The extracts of mistletoe lectin is composed of three different lectin types i.e. mistletoe lectin I, II, and III, however, the difference in each of them is yet to be identified. The clinical trials carried out using human breast cancer cells using *Viscum album* var. coloratum agglutinin (VCA), a purified lectin from Korean mistletoe, gave positive outcome. When this lectin was combined with doxorubicin (DOX), the PCD events were stronger. The combined effects were due to inhibition of Bcl-2 and induction of Bax and Puma proteins that induces apoptosis. It is also studied that Korean mistletoe triggers p53 and p21-independent pathways in human hepatocarcinoma cells by blocking the BCl-2 and telomerase activities and activating the Bax functioning thus induces apoptosis (Yau et al. 2015).

Another lectin, Concanavalin A (ConA) is extracted using jack bean seeds. Human melanoma A375 cells when treated with ConA, experienced the caspase-dependent apoptosis via mitochondrial apoptotic pathways. It is observed that the level of cytochrome c got enhanced that activated the caspase-9 and caspase-3. Another study reported that ConA elicited autophagy in HeLa cells by activating the MEK/Extracellular signal-regulated kinases (ERK) pathway and blocking the membrane-mediated phosphatidylinositol 3 kinase/Akt/mTOR (mammalian target of rapamycin) pathway (Yau et al. 2015).

Polygonatum odoratum lectin (POL) induces apoptosis signals like DNA fragmentation, volume reduction and membrane blebbing in A549 lung cancer cells. POL belongs to GNA-related family lectins which shares common 3D structures even after having a different primary amino acid sequence. Because of having specific amino acid sequences, all the lectins of the family binds to monosaccharide mannose.

POL induces apoptosis by blocking the Akt-NF-κb pathway involved in mitochondrial-mediated pathway while in induces autophagy by suppressing the Akt-mTOR pathway. It is also noted that it induces the caspase- dependent pathway in L929 rodent cells and augments the action of TNFα, a tumor necrosis factor (Yau et al. 2015). In another example, Soybean (Glycine Max) lectin generates reactive oxygen species (ROS) to induce DNA damage, apoptosis and autophagy in HeLa cancer cell lines.

Additionally, marine animal lectins are also gaining scientific interests and tested for their anticancer properties. For instance, European seabass or Dicentrarchus labrax fucose-binding lectin (DIFBL) which is present in larvae of the *Dicentrarchus labrax.* fish after one month of hatching. DIFBL showed promising results in a variety of cancer cell lines viz. lung cancer cell lines (A549), liver cancer cell lines (Hep3B, BEL-7404) and colorectal carcinoma cell lines (SW480). The apoptosis was induced through suppressing the expression of Bcl-2 and XIAP, anti-apoptosis factors in Hep3B cells (Yau et al. 2015).

Sialic Acid Binding Haliotis Discus Discus Lectin (HddSBL) also showed effective anticancer activities against lung (A549 and H1299), liver (Hep3B) and colorectal carcinoma (SW480) cancer cells. It was extracted and purified from *Haliotis discus discus* which is also known as disk abalone. Study done using HddSBL lectins showed that it suppresses the Bcl-2 expression but not activated that capases (cysteine-dependent aspartate-directed proteases) which are crucial protein and plays role in apoptosis induction (Yau et al. 2015).

Promoting Autophagic Necrosis Pathways with/without Necrobiosis

The process of destroying its own organelles through lysosome or autophagosome is known as autophagy. It can be microautophagy and macroautophagy of which generally autophagy is concerned with macroautphagy. In case of macroautophagy, an autophagosome is created by separating part of the cytoplasm and thus a separate vesicle is created while in microautophagy, lysosome directly enwrap and transport the cargo into the lumen of lytic organelles.

Autophagy is a survival strategy that has evolved over time the distruction and restoration of redundant macro-complexes in eukaryotic cells. Plant lectin cause autophagic cell death with/without apoptosis in cancer cells (Tyagi et al., 2015).

Liu and colleagues reported that ConA activates the BNIP3-mediated mitochondrial pathway to induce the autophagy in carcinoma cells (Liu et al. 2009A). Another study suggests that ConA initiates the autophagic pathways in heptatome ML-1 cells by binding to the mannose glycoproteins (Yau et al. 2015). PCL activates the mitochondrial ROS-p38-p53 pathway A375 cancer cells to induce autophagic death pathway (Liu et al., 2009B; Shi et al., 2017).

5. CONCLUSION

Plant lectins has given an enormous contribution in advancing the therapeutic applications in cancer biology. Unquestionably, plant lectins can endure having a significant role as components thanks to their specific carbohydrate-binding property. The understanding of their sugar-binding specificity and also the 3D structures might permit the lectins to be built to spot specific glycoconjugates. This can facilitate the researchers to analyze the exceptional part of carbohydrates that play in cell-cell interactions, cellular regulation and additionally play a vital role in an exceedingly higher understanding of the biological roles of those attention-grabbing plant proteins. It has been well recognized that dysfunctional

growth neovascularization has been critically attributed to growth and progression. Thus, suppression of growing cell and induction of necrosis has been determined as a placing strategy to focus on cancer progression. Plant lectins have fascinated a lot of attentiveness due to their capability to activate multiple biological processes. The potential of plant glycoproteins, of activating the immune pathways rendering them valuable tools within the field of cancer research. These three-dimensional actions of lectins make a case for their effectiveness as single agents against varied malignancies.

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Section 3

Antioxidant Natural Products as Cancer Therapeutics

Chapter 18
Anticancer Properties of Some Antioxidants

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ABSTRACT

The purpose of this chapter is to reveal the important properties of some anticancer antioxidants. Cancer can be defined as a disease caused by very different cell types and organs of the human body and characterized by very fast growth and the ability to metastasize to other organs. Cancer cells typically exhibit higher levels of basal ROS than normal cells, mainly due to their increased metabolism, oncogene activation, and mitochondrial dysfunction. Antioxidant system is a form of defense against high ROS production in cells. Quercetin plays an important role in the prevention and treatment of many types of cancers. Resveratrol is considered a potential candidate for the prevention and treatment of many types of cancer. Antioxidants such as CAPE, Quercetin Resveratrol, which have antioxidant properties and destroy ROS, may be a promising treatment strategy in cancer. Antioxidants are thought of as popular natural remedies that are used by the majority of people and have few side effects. However, even with the available data, more experimental and clinical studies are needed.

INTRODUCTION

All types of cancer occur as a result of the changes in the DNA sequence of the genomes of cancer cells. Cancer can be defined as a disease caused by very different cell types and organs of the human body and characterized by very fast, unlimited proliferation of cells that exceed normal tissue boundaries and can metastasize to other distant organs (Hussain, 2003). Although information about diseases and treatment experience have progressed tremendously around the world, unfortunately, the prevalence and mortality rate from cancer continue to increase. Eating habits and lifestyle are probably an easy, fast and practical way to protect yourself from cancer that requires less finance. Before cancer treatment, it has been reported that food and nutrition, one of the ways to prevent the development of a tumor, can be

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important factors for the development or reduction of cancer risk and can prevent cancer by 30% to 40%. The literature has specifically mentioned compounds with antioxidant properties and their positive aspects (Russo, 2017). Almost 10 million people died from cancer in 2020 while the number of new cases of cancer in the world was about 19.3 million in 2020. Breast cancer became the most diagnosed cancer in 2020, surpassing lung cancer. Female breast cancer ranks first with 2.3 million new cases, with an estimated rate of 11.7%, followed by lung cancer with an estimated 2.2 million new cases, 11.4%, colorectal cancer ranks third with 1.9 million new cases with a rate of 10.0%, prostate cancer is fourth with 1.4 million new cases, 7.3%, and stomach cancer is fifth with more than 1 million new cases with a rate of 5.6%. Lung cancer, which is most common in men, is also the most important cause of cancer-related deaths in men. Breast cancer, which is most commonly diagnosed in women, is also the most important cause of cancer-related deaths in women. The 10 cancer types, which are the most common types of cancer in the world, forms more than 60% of newly diagnosed cancer cases and more than 70% of cancer deaths. It is estimated that 28.4 million cases of cancer (including Nonmelanoma Skin Cancer excluding basal cell carcinoma) will be detected in 2040, which is expected to be a 47% increase compared to 2020. Overall, the cancer incidence and the burden of mortality worldwide is increasing rapidly (Sung, 2021). Along with the medical ailments caused by this burden, the struggle from social, material and spiritual aspects makes it a difficult disease. It is expected that it will create a burden that cannot be overcome in the following years around the world. (https://www.who.int/health-topics/cancer#tab=tab_1). Alternative drugs for cancer treatment are a multibillion-dollar industry. 30% -50% of cancer deaths are caused by preventable risk factors. Getting away from them and reducing these risk factors significantly reduces the burden of cancer. Smoking-tobacco use is the most serious risk factor, accounting for almost 25% of the world's cancer burden as the cause of 22% of deaths (Feigin, 2016). There are thousands of agents that are known to play a role in the etiology of cancer or have not yet been illuminated. Smoking-tobacco use is the most common and serious risk factor, especially in the development of lung cancer, with a rate of 70%. It also plays a role in the etiology of cancer of the esophagus, oral cavity, gastrointestinal tract and cervix (Wild, 2014). There is a striking association between the progression of age and the increased incidence of cancer (DePinho, 2000). It has been shown to be involved in the etiology of obesity, post-menopausal breast cancer, and endometrium, pancreas, colorectal, renal cell cancer (Renehan, 2008). A significant increase in the prevalence of known cancer risk factors (smoking-tobacco use, unhealthy diet, excessive body weight, alcohol intake, physical inactivity, increased intake of animal-derived foods, pickled-canned foods, smoked products, saturated fats, processed foods, inadequate whole grain consumption, insufficient fiber consumption, insufficient dairy product consumption, low fruit intake, excessively processed meat consumption, grilled or barbecued meat and fish consumption, aflatoxin exposure) are experienced in many countries. Refined sugar consumption provides the basis for cancer by causing obesity, by affecting the process leading to cancer with insulin resistance and subsequent desensitization. Sedentary lifestyle accelerates the development of cancer. Infections such as Hepatitis C-B,Human papillomavirus, Helicobacter Pylori are responsible for almost a quarter of cancers, especially in developing countries. Chemical agents and drugs, ionised radiation, ultraviolet rays again play a role in the etiology of cancer. (Sandhu, 2001; Sung, 2021). Increasing evidence in recent years draws attention to reactive oxygen species (ROS), which have become an important factor in the regulation of cellular stages that regulate tumor formation (Stortz, 2005) It is the mitochondria that contributes the most to the endogenous ROS pool (Handy, 2015; Qiunlan, 2012). It may have a detrimental role as well as the cellular signaling properties of ROS, produced from complexes I and III in the electron transport chain. The release of mitochondrial ROS may contribute to the initiation and

progression of different types of cancer. Lymphocytic leukemia, acute myeloid leukaemia and breast cancer include some of the cancer cases associated with high levels of mitochondrial ROS (Hart, 2015; Murphy, 2009; Moloney, 2017). High sources of ROS such as NADPH oxidases (NOX), the first family of enzymes that produce ROS, and lipoxygenases other than mitochondria, xanthine oxidases, cytochrome p450 enzymes, and nitric oxide synthases are associated with cancer (Moloney, 2018). ROS levels resulting from high NOX are involved in the transformation and progression of many common cancers, including lung, breast, kidney, bladder, leukemia, melanoma, ovarian, pancreatic, esophageal, prostate, stomach, colon and thyroid (Block, 2012). There are opinions arguing that ROS have a role as a tumor suppressor in addition to being a tumor promoter. But this article will discuss more about the tumor-promoting part (Chio, 2017). Highly reactive ROS are radicals, ions, or molecules that have one unshared electron in their outermost electron shell. ROS are divided into two groups: free oxygen radicals and non-radical ROS. Structures such as hydroxyl radical (•OH), superoxide (O2•−), nitric oxide (NO•), organic radicals (R•), alkoxyl radicals (RO•), thiyl radicals (RS) are present•), sulfonyl radicals (ROS•), thiyl peroxyl radicals (RSOO•), and disulfides (RSSR) are defined as superoxide radicals. It is defined as ROS without hydrogen peroxide (H2O2), singlet oxygen ($^1O_2$), ozone/trioxygen (O_3), organic hydroperoxides (ROOH), hypochlorite (HOCl), peroxynitrite (ONO−), nitrosoperoxycarbonate anion ($O{=}NOOCO_2^-$), nitrocarbonate anion ($O2NOCO_2^-$), dinitrogen dioxide (N_20_2), nitronium (NO2+) and carbohydrate-derived carbonyl compounds or highly reactive lipid radicals. Increased production of ROS has been detected in various types of cancer. High levels of ROS are oncogenic, causing cell damage, enhanced cell proliferation, cell death, autophagy, genetic instability, damaging DNA, proteins and structural and/or functional properties of macromolecules such as lipids, mitogen-activated protein kinase (MAPK)/ thought to promote the pathway of regulation of extracellular regulated kinase. Tumor cells have a differentiated redox balance compared to normal cells. Therefore, antioxidant defense mechanisms and specific modifications of ROS generation are identified as important targets in cancer treatment (Chio, 2017; Moloney, 2018; Zorov, 2014). Overproduction of ROS, which is associated with an increase in DNA damage, is important for genetic instability. DNA damage in cells that affect the interpretation and transmission of genetic information in DNA refers to physical or chemical changes. DNA damage causes oxidation of DNA, resulting in various changes, including deletions, insertions, base pair mutations, and double chain fractures resulting in translocations, one of the most damaging lesions. In addition, ROS oxidize nucleoside bases that directly induce DNA damage forms, (e.g., 8-OHdG) can lead to G-T or G-A transversions if these forms of damage are not repaired (Karanjwala, 2002; Srinivas, 2019). Studies in solid tumors have shown that 8-OHdG levels, one of the products of oxidative damage, with a mutagenic character and high sensitivity for immunological detection, are high in solid tumors. High levels of 8-OHdG have been demonstrated in squamous cell carcinoma, non-small cell lung cancer, thyroid neoplasia, and prostate cancer cells (Young, 2010; Barrera, 2012). Oxidative modification of proteins attacked by reactive species plays a role in the etiology or progression of numerous disorders and diseases. ROS' damage to proteins results in the changing functions of proteins after the change of proteins in amino acid residues. Some ROS-triggered modifications increase nitration of tyrosine and phenylalanine residues, protein carbonylation, protein degradation, or lead to the formation of cross-linked and glike proteins (Levine, 2002; Squier, 2000). The p53 protein, which provides a major barrier to neoplastic transformation and tumor progression, is a known tumor suppressor that mutates in more than 50% of all cancers and affects multiple cellular responses to DNA damage. The p53 protein, which has cysteine residue clusters and is a redox protein, takes part in regulating ROS as well as being the target of ROS. In addition, p53 has an important role in the regulation of pro and antioxidant genes

depending on the density of ROS. p53 has been shown to reduce ROS accumulation by controlling the expression of antioxidant enzymes such as SOD2, catalase and GPX1 . (Humpton, 2016; Kruiswijk, 2015; Maillet,2012; Mantovani,2019). Lipids are the key cellular target site of ROS, ROS react with fatty acids containing high levels of PUFA in membrane phospholipids to initiate lipid peroxidation. Lipid peroxidation plays a critical role in cell death, including autophagy, apoptosis, and ferroptosis. Lipid peroxidation shows high biological activity, producing a large number of genotoxic molecules such as chain reaction products 2-alkenals, malondialdehyde and 4-hydroxy-2-alkenals (Su, 2019; Unsal, 2020). The lipid peroxidation products produced play an important role in inducing mutations responsible for DNA modifications that trigger carcinogenesis (Voulgaridou, 2011). The use of antioxidants has been recommended for a potential therapeutic intervention against oxidative stress, which has an important role in the development of cancer by producing ROS-induced lipid peroxidation (Morry, 2017). Also increased ROS are involved in the induction of autophagy, one of the first defenses against oxidative stress damage. Autophagy is a lysosomal pathway associated with the degradation and recycling of proteins and organelles within the cell, which is important for cellular homeostasis (Li, 2012; Gibson, 2010). ROS inactivate or increase the prevalence of the protein Bcl-2, which is anti-apoptotic. It can induce apoptosis, defined as type I programmed cell death, and necrosis, defined as type III programmed cell death (necroptosis), by reducing intracellular levels of Bax and Bad. (Luanpitpong, 2013; Galluzzi, 2008; Vandenabeele, 2010). In response to ROS and oxidative stress, cells use various adaptation mechanisms. Antioxidant system is a form of defense against high ROS production in cells. Antioxidant system activity is up-regulated to maintain redox balance of increased ROS levels (Janssen, 1999; Miranda, 2000; Toledano, 2010). Antioxidants, which are important in tumor development, can prevent the effects of ROS early (Liou,2010). The high death rate of cancers makes it essential to find new anticancer treatments to prevent cancer. Phenolic compounds are phytochemicals that are naturally found in fruits, vegetables, grains and various plant products and are responsible for various characteristic features of these foods such as color, taste and smell. Phenolic compounds are divided into two classes, flavonoids and non-flavonoids (Shadidi, 2016). Non-flavonoids; phenolic acids (C6-C1; caffeic acid, gallic acid, etc.), stilbenes (C6-C2-C6; resveratrol, piceid, etc.) and lignans (C6-C3-C3-C6). In the flavanoids group, there are subgroups that also include flavanols (catechin, proanthocyanidins, etc.), flavonols (quercetin, myricetin, etc.) and anthocyanidins (cyanidin, malvinidin, etc.) (Albishi, 2013). Phenolic compounds play an important role in maintaining the balance between oxidants and antioxidants in the body (Acosta-Estrada, 2014). All flavonoids have antioxidant activity with 3-4 dihydroxy configuration. Flavonoids and other plant phenolics have functions of scavenging radicals such as superoxide, alkoxyl, peroxyl and nitric oxide, iron and copper chelation, μ-tocopherol regeneration. In addition, flavonoids and other plant phenolics have vasodilator, immunostimulant, antiallergic, estrogenic, antiviral effects (Bohn, 2014). Phenolic compounds (Hydroxybenzoic Acids, Hydroxycinammic Acids, Coumarins, Xanthones, Chalcones, flavonoids, phenolic acids, tannins, stilbenes, and lignans) prevent the opening of new vessels (angiogenesis), which is necessary for the growth of tumors, as well as strengthen the body's immune system to recognize and destroy cancer cells. These compounds show inhibitory action against the development of several serious diseases such as cancer, Alzheimer's and diabetes (Rice-Evans, 1997; Anantharaju, 2016; Albuquerque, 2021). ROS, which contribute to malignant transformation, allow the tumor to begin, develop and progress. Although whether antioxidants prevent or promote cancer is still controversial in human health, there is much more evidence that antioxidants prevent cancer. But antioxidants are favorite candidates in both prevention and treatment of cancer, as they can destroy or extinguish ROS and reduce oxidative stress (Vafa,2002; Teoh-Fitzgerald, 2014). Nrf2, a transcription

factor, is activated to increase the production of antioxidant proteins in tumor cells and maintain redox homeostasis. Structural upregulation of this transcription factor was reported for various types of human cancers, including skin, breast, prostate, lung, and pancreas (No, 2014). Angiogenesis, or the production of new blood vessels, is a critical process in metastatic growth of cancerous tissues, and high concentrations of antioxidants were found in cancer models to suppress angiogenesis (Liu, 2013; Powolny, 2005; Ito, 2011). Therefore, inhibiting pro-tumorigenic signaling pathways as a result of suppressing ROS activity or increasing its antioxidant capacity, which maintains the reduction-oxidation (redox) balance, may be an important approach for ROS to treat cancer. Detoxification of ROS is carried out by enzymatic or non-enzymatic antioxidants involved in the cleansing of different types of ROS. CAPE, Quercetin, Coenzyme Q10, Melatonin, Curcumin, Resveratrol, α-Lipoic acid, Glutathione, flavanoids, vitamin A, C and E can be given as examples of non-enzymatic antioxidants. Superoxide dismutase (SOD), superoxide reductase (SOR), Catalase (CAT), glutathione peroxidase (GSH-PX), glutathione reductase (GR), peroxiredoxin (PRX) and thioredoxin (TRX) are enzymatic antioxidants (Dickinson, 2011; Unsal, 2020)

CAFFEIC ACID PHENETHYL ESTER (CAPE)

CAPE is a major bioactive compound of propolis extract. Propolis is a substance whose content differs depending on geographical location, is easily available, cheap, has been used for many years in traditional medicine for its therapeutic properties. It is now sold as a dietary supplement (Omene, 2013). CAPE has antimicrobial, antioxidant, free radical scavenger, antiinflammatory, antiviral, immunostimulatory, antiangiogenic, antimetastatic, fungicide, antiinvasive, carcinostatic activity and cytotoxic properties (Song, 2007; Vagish, 2014). CAPE obtained from propolis by extraction from honey bee hives, its chemical name is 2-phenylethyl (2E)-3-(3,4-dihydroxyphenyl) acrylate. Its molecular formula is $C_{17}H_{16}O_{4}$,(Lv, 2021; Kumazawa, 2010). CAPE is a formidable anti-cancer agent that kills cancer cells, while CAPE is noteworthy that it is harmless to normal cells. It suppresses the proliferation of many human cancer cell lines, such as head and neck, breast, cervical prostate, lung. It regulates factors such as apoptosis and necrosis in various cancer cells, induces cell cycle arrest (G1 or G2/M), increases the activity of p53 protein, and suppresses cancer cell movement and migration. In different animal models, CAPE given orally or injected intraperitoneal was shown to prevent cancer onset, tumor growth, cancer metastasis (Wu, 2011; Kuo, 2015; Lin, 2006; Ulasli, 2013). Human pancreatic and colon cancer cells undergo apoptosis in the presence of CAPE, it exerts an antiproliferation effect, and up-regulates the activation of caspase-3 in human leukemic HL-60 cells, downstream of Bcl-2 and up-regulates Bax. In addition, CAPE was shown to inhibit a protein NF-κB, which is high in cancers (such as squamous head and neck carcinomas), influencing the activity of important proto-oncogenes, promoting the growth and survival of altered cells during the cell cycle. Agents that down-regulate the activation of NF-κB are thought to have significant potential in therapeutic interventions. So the CAPE is considered a good candidate. (Chen,2006; Xiang,2006; Samet, 2007; Murtaza, 2014). CAPE suppresses vascular formation by inhibiting Vascular Endothelial Growth Factor (VEGF) and suppresses tumor invasion and metastasis by matrix metalloproteinases (MMPs) (Wu,2017). Firat et al. reported that CAPE suppresses angiogenesis in colon and breast cancer cells (Fırat, 2019). A dose-related decrease in cell viability in colon adenocarcinoma cells (CT26) was reported with CAPE therapy. Again, in CT26 cells, but in a different study, it was reported that CAPE reduced both MMP expression and VEGF production, reducing angiogenesis

and metastasis (Liao, 2003; Lofty, 2006). It was reported that CAPE inhibited breast cancer cell growth in two different breast cancer cell lines, MDA-231 and MCF-7, due to its effects on tumor cytotoxicity, apoptosis, cell cycle, NF-κB and angiogenesis. CAPE down-regulates the mdr-1 gene, which is thought to be responsible for the resistance of cancer cells to chemotherapeutic agents. It was shown to strongly inhibit the formation of blood vessels that occur in solid tumors even under hypoxic conditions. (Wu, 2011).

Rb is a tumor suppressor protein that is mutated and suppressed in various types of cancer. The reduction in phosphorylation of Rb inhibits the activity of E2F transcription factors and thus limits cell proliferation. Moreover, loss of Rb function can trigger either p53-dependent or p53-independent apoptosis, as Rb abundance in TW2.6 cells is also suppressed by CAPE treatment. In addition, CAPE therapy increases tumor suppressor activities by reducing the phosphorylation of FOXO1 and FOXO3a (Murphree, 1984; Chellappan, 1991; Harbour, 2000). Breast cancer cells express estrogen receptors (ER), whereas estrogen has potent proliferative effects, affecting differentiation and survival. Er+MCF7 cells treated with estrogen receptors and an estrogen response gene CAPE were shown to down-regulate both ER and PR (Zhou, 2006; Davidson, 2000; Hurvitz, 2008). By inducing autophagy and apoptosis under inflammatory conditions, CAPE inhibits the toll-like receptor 4 (TLR4) signaling pathway, which contributes to breast cancer pathogenesis. In addition, CAPE interferes with the growth of breast cancer stem cells by suppressing their self-renewal and reducing CD44 levels (Chang, 2017; Omene, 2012). In addition to inhibiting proliferation in human colorectal cancers, CAPE can block cell cycle progression and induce apoptosis by reducing expression of β-catenin. It also suppresses the invasion and motility of cancer cells, can promote autophagy in cultured colon cancer cells by altering the expression of multiple genes. (Budisan, 2019). It significantly increases the levels of Bax, CytoC, P53 and p38 in the HT-29 cell line (Tang, 2017). Although CAPE reduces the colony forming ability of metastatic NCaP, DU-145 and PC-3 prostate cancer cells, which are widely used in research, it was observed that these cells suppress proliferation depending on the dose (Borrelli, 2002; Liu, 2013). CAPE suppresses cell proliferation, colony formation and cell cycle progression by inhibiting protein kinase B (Akt)-related pathways in a variety of human prostate cancer cells, and can significantly inhibit tumor growth in vivo (Chuu,2012). CAPE can reduce the viability, migration and invasion of ovarian cancer cells and induce apoptosis by suppressing in vivo NF-κB signaling (Liu, 2018). It was also reported that it inhibits the S- and G2/M-phase cell cycle in human cervical cancer cells and initiates apoptosis by upregulating the expression of the E2 factor transcription factors 1 family. It can inhibit cell proliferation by regulating the activator of the signal transducer and transcription (STAT)-3/Polo-like kinase 1 pathway (Hsu, 2013; Ren, 2019). In a study by Kleczka et al., CAPE exhibited dose- and time-dependent cytotoxic activity against OV7 serum ovarian cancer cells and induced apoptosis through dysregulation of the Bax/Bcl2 balance (Kleczka, 2020). Breast cancer research studies showed that CAPE is an inhibitor of FGF-2 (fibroblast growth factor type 2), a factor of tumor growth (Kabala, 2017). CAPE selectively destroys cancerous cells without damaging normal cells (non-cancerous cells) in human immortal lung fibroblast WI-38 cells (Chen, 2004). In a study investigating the effect of CAPE on the lung cancer A549 cell line, it was found that CAPE suppresses motility supported by TGF-β-induced Akt phosphorylation (Shigeoka,2004). Multiple myeloma cells were shown to be sensitive to the antiproliferative and proapoptotic properties of CAPE (Marin, 2019). Release of mitochondrial cytochrome c, activation of caspase-3 and increase of Bax gene expression in human myeloid leukemia U937 cells exposed to CAPE led to simultaneous silencing of Bcl2 activity (Jin,2008). In light of these findings, CAPE seems to be a candidate to be a promising natural product for anticancer application.

QUERCETIN

Quercetin, a polyphenolic flavonoid compound, known chemically as 3,3',4',5,7-pentahydroxyflavone, ($C_{15}H_{10}O_7$) plays an important role in the prevention and treatment of diseases such as many types of cancers, cardiovascular and neurodegenerative diseases due to its strong antioxidant, anticancer, anti-allergic, anti-diabetes, anti-ulcer, anti-viral, anti-aging, anti-inflammatory properties. Quercetin, which has a variety of biological activity, is abundant in red grape, apple, onion, honey, raspbery, cherry, citrus fruits and leaf vegetables. Quercetin reduces oxidative stress by controlling the oxidant-antioxidant balance, increasing the levels of endogenous antioxidants. Quercetin regulates the level of GSH in increasing the body's antioxidant capacity. Due to the effect of Quercetin on ROS, which is considered a toxicological factor, it maintains oxidative balance by demonstrating strong antioxidant activity. Quercetin regulates both the internal and external pathways of ROS-mediated protein kinase C (PKC) signaling, which induces apoptosis in cancer cells. In addition, it prevents cancer development by upregulating the tumor suppressor p53 and exerts direct proapoptotic effects on tumor cells (Lacopetta, 2017; Lesjak, 2018; Xu, 2019; Rauf, 2018; Batiha, 2020, Hashemzaei, 2017; Vafadar, 2020; Jia, 2018). The antioxidant effects of quercetin create proapoptotic effects through various mechanisms, including suppression of the p53 gene and BCL-2 gene transcription. In addition, quercetin increases nucleus fragmentation, number of cells in the lower G1 phase, degradation of poly(ADP-ribose) polymerase protein, activation of caspase-3 and caspase-9, induces intrinsic apoptosis through translocation to mitochondria (Hsu, 2008; Reyes-Farias, 2019). In the case of oxidative stress, it makes cells susceptible to H_20_2damage when p53 is reduced, which is necessary to reduce intracellular ROS concentrations. Quercetin reduces ROS elevation by raising p53 levels, which are down-regulated in cancer cells (Gibellini, 2011). Quercetin, a potent ROS scavenger and electron donor, inhibits the release of cytokines by reducing ROS levels and DNA damage, inhibiting lipid peroxidation, reduces the production of COX and LOX and maintains the stability of mast cells, thanks to these properties, it undoubtedly shows strong anti-inflammatory effects (Pérez-Cano,2016; Dower, 2015; Shafabakhsh, 2019). Quercetin inhibits the production of tumor necrosis factor (TNF)-α, an important pro-inflammatory molecule involved in chronic inflammatory diseases that can develop into tumors. Repressed TNF-α inhibits NF-KB activation, enabling the stimulation of anti-inflammatory cytokines (Nair, 2006). Targeting the VEGFR-2-mediated angiogenesis pathway, suppressing the expression of the downstream regulatory factor AKT and limiting tumor growth, quercetin exerts an inhibitory effect on angiogenesis (Pratheeshkumar, 2012; Balakrishnan, 2016). The expression level of heat shock proteins (HSPs), which are found high in almost all types of cancer, involving in cell proliferation and leading to cell apoptosis, is high. Quercetin reduces the transcription and translasyon of HSP27 and 72 in the T98G cell line (Bądziul, 2014; Lee, 2012). Quercetin was shown in a study that it inhibits the growth of different cancers in various xenograft models, significantly reducing the tumor volume of tumor-carrying animal models, seriously increasing the survival rate of animals (Tang, 2020; Maso, 2014). Quercetin induces P21, a cycline-dependent kinase (CDK) inhibitor, by inducing mild DNA damage and Chk2 activation, thereby inducing G1 cell cycle stop. It also inhibits DNA synthesis, stops the cell cycle in the S phase (Jeong, 2009; Haghiac, 2005). In MCF-7 and MDA-MB-231 breast cancer cell lines, quercetin suppressed cell proliferation by suppressing tumor growth, by inducing apoptosis, stopping the G1 phase in the cell cycle. In addition, by modulating Akt and Bcl-2-associated X protein (Bax) signaling mechanistic pathways, by significantly suppressing the expression of Twist, CyclinD1, p21 and phospho p38 mitogen-activated protein kinases (p38MAPKs), it causes cell cycle arrest and apoptosis in breast cancer cells. In addition, quercetin increases FasL mRNA expression,

P21, P51, growth arrest, and 45 (GADD45) signaling activities that can be induced by DNA damage (Liao, 2015; Ranganathan, 2015; Sarkar, 2016). In a study aiming to examine the effect of quercetin on tumor metastasis, cell glycolysis, and its associated functional mechanism in breast cancer progression, it was reported that quercetin effectively suppresses breast cancer cells' invasion, migration ability, the progression of breast cancer by inhibiting in vivo glycolysis, cell mobility via AKT-mTOR pathway-mediated autophagy induction, by suppressing the expression of MMP-3, MMP-9 and VEGF, which are important proteins associated with tumor metastasis (Jia, 2018). In a study, it was reported that Quercetin can inhibit cell viability of colon 26 (CT26) and colon 38 (MC38) cells, induce apoptosis in CT26 cells through the MAPKs pathway, and regulate the expression of EMT markers (Kee, 2016). In another study, it was observed that quercetin suppressed the NF-κB pathway of quercetin in CACO-2 and SW-620 colon cancer cells, down-regulating B-cell lymphoma 2 and up-regulating Bax, thereby seriously stopping its proliferation (Zhang, 2015). Quercetin was found to be an inhibitor of Wnt/β-catenin in SW480, DLD-1 and HCT116 colon cancer cells (Amado, 2014). It was shown that in human pancreatic cancer cell lines, quercetin suppresses migration activity caused by epidermal growth factor, exerts antitumor effect, significantly inhibits proliferation, promotes apoptosis, induces cell cycle arrest in G1 phase, selectively inhibits EGFR-mediated focal adhesion kinase, protein kinase B (AKT), MEK1/2 and ERK1/2 signaling pathway, significantly inhibits MMP-2 and -9 expression, aldehyde dehydrogenase 1 activity, colony and spheroid formation (Appari, 2015; Lee, 2015; Chen, 2015). Quercetin shows antitumor activity in hepatocellular carcinoma cell line HepG2 cells both in vitro and in vivo, increasing p53 and Bax expression (Maurya, 2015). In different studies, it was reported that in human lung cancer JB6 Cl41 and A549 cells, quercetin significantly suppresses cell invasion, cell growth and migration, inhibites aurora B activities, decreases histone 3 phosphorylation, induces apoptosis, MMP-9 (mRNA and protein), reduces TGF-β1 protein, causing an imbalance in the Bcl2/Bax ratio that can lead to mitochondria-mediated apoptosis (Zhao, 2015; Xingyu, 2016; Mukherjee, 2015). It was found in another A549 lung cancer cell line study that quercetin triggers apoptosis, as well as necrosis and the mitotic process, and suppresses the migration of these cells through regulation of BCL2/Bax (Klimaszewska-Wiśniewska, 2017). In human prostate cancer cell lines such as PC3 and LNCaP, quercetin induced apoptosis leading to cytochrome c release, cleavage of caspase 3, PARP, and triggered cell cycle arrest. It also inhibits the generation of ROS and Akt/mTOR cell survival pathways in PC-3 cells (Song, 2016; Hamidullah, 2015). It was reported that cell viability decreased after 40 μM quercetin treatment in prostate cancer (Pca) cells, necrosis increases after apoptosis, quercetin has impressive effects on mitochondrial integrity, depending on the oxidation state of cells, quercetin can act as an antioxidant or a pro-oxidant to balance ROS production in PCa cells (Vafadar, 2020). Treatment of the human osteosarcoma cell line 143B with quercetin resulted in major growth inhibition, cell proliferation inhibition, G2/M phase arrest, apoptosis, upregulation of miR-217 expression, downregulation of target KRAS at both mRNA and protein levels (Berndt, 2013; Zhang, 2015). In a study by Chen et al., it was reported that in U937 human leukemia cells, quercetin inhibits cell proliferation synergistically, induces apoptosis by decreasing the Bcl2-Bax ratio, significantly reduces the phosphorylation stages of downstream signaling proteins AKT and mTOR, inhibits expression of the heat shock protein HSP27. In the light of these findings, it was concluded that quercetin shows anticancer properties in U937 human leukemia cells (Chen, 2016). It revealed that quercetin exhibited pronounced apoptosis, Bcl-2, Bcl-xL, and down-regulation of myeloid cell leukemia (Mcl)-1, up-regulation of Bax, and mitochondrial translocation in P39 leukemia cells, induced expression of FasL protein and produced amplified cell arrest in the G1 phase of the cell cycle (Maso, 2014). Treatment with quercetin significantly reduces both caspase-3

activity and the proportion of apoptotic cells in human K562 chronic myeloid leukemia cells, altering the cell cycle profile, increasing Bcl-2 protein expression, and stopping the downregulation of Mcl-1 and Bcl-xL (Brisdelli, 2014). It was found in a study in which different concentrations of quercetin were applied, quercetin significantly reduced cell viability in human malignant pleural mesothelioma cells (MSTO-211H), induced apoptotic cell death, increased the lower G_1 cell population, and interacted with Sp1 and significantly inhibited its expression at protein and mRNA levels (Chae, 2012). U87-MG glioblastoma suppressed the dose-dependent cell viability of quercetin in different cell lines, such as U251 and SHG44 glioma. It was found that in these cell lines, quercetin significantly reduced glioma cell migration and increased cell aging and apoptosis, it significantly reduced the protein concentrations of p-AKT, p-ERK, MMP-9, Bcl-2 and fibronectin, also suppressed Ras/MAPK/ERK and PI3K/AKT signaling pathways (Pan, 2015). Treatment of A2780S cells with quercetin was found to induce apoptosis, stimulate caspase-3 and caspase-9, downregulate MCL-1 and Bcl-2, upregulate Bax, and alter mitochondrial transmembrane potential (Gao, 2012). It was reported that quercetin administration significantly delayed growth in HeLa cells, induced apoptosis in a time- and dose-dependent manner, caused cell cycle arrest in the G0/G1 phase, down-regulated the expression of PI3K and p-Akt, down-regulated the expression of bcl-2, up-regulated Bax (Xiang, 2014). In addition, quercetin induces DNA fragmentation and comet formation in HeLa cells, inducing cell cycle arrest. It modulates the expression of pro- and anti-apoptotic proteins, reduces cell migration (Kedhari, 2019). In the ovarian cancer SKOV-3 cell line, it was revealed that quercetin significantly suppressed the proliferation of cells, promoted apoptosis, decreased survivin protein expression, triggered cell cycle arrest in G0/G1 and a remarkable decrease in cell ratio in G2/M phase (Ren, 2015). The WNT signaling pathway, which regulates tumor progression and migration, plays an important role in cervical cancer, reduces the expression of WNT signaling pathway elements WNT2 and CTNNB1 through quercetin. In addition, quercetin down-regulates structures such as TGFβ1, SMAD2, SMAD3 and SMAD4 (Zhou, 2016). Quercetin was shown to significantly reduce cell proliferation and improve apoptosis rate with caspase activation, induce cell apoptosis through down-regulation of Hsp90 expression, suppress growth and cause cell death in human papillary thyroid cancer cells (Mutlu, 2014).

RESVERATROL

Resveratrol (3,4′,5-trihydroxy-trans-stilbene), which is a stilbene-based and non-flavonoid polyphenol in its natural structure, is a phytoestrogen with antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, anti-angiogenesis, neuroprotective, immunomodulatory, glucose and lipid regulator, which are found naturally in many plant species such as peanuts, grapes, pine, and strawberries, having cardioprotective and anti-cancer properties. Promising for many reasons, resveratrol is cheap and easily available, making itself advantageous. It contains two phenolic rings with its bond connected by an ethylene bridge, both trans - resveratrol and cis - resveratrol occur in isomeric form. Due to the property of naturally occurring phytoalexin, a substance synthesized de novo by plants, it is effective against pathogens, including bacteria and fungi. Resveratrol is also available in processed products such as wine, apart from the plants mentioned above. Resveratrol, which is abundant in the content of wine, is attributed to the fact that moderate consumption of red wine reduces the risk of coronary heart disease. In addition to the phenolic rings with three hydroxyl (OH) groups in the 3, 4’ and 5 positions of the phenolic rings in its structure and the conjugated double bond, the electron delocalization potential in the structural mol-

ecule, its radical scavenging, metal ion chelating abilities significantly affect the antioxidant properties of resveratrol (Meng, 2020; Singh, 2015; Salehi, 2018; Ko, 2017; Truong, 2018). Apart from radicals induced by metals/enzymes and produced by cells, Resveratrol is an excellent scavenger of oxidants such as superoxide anion, hydrogen peroxide, hydroxyl radical, singlet oxygen, nitrogen oxide and peroxynitrite. In addition, resveratrol provides serious protection on various redox-related molecular pathways against lipid peroxidation in cell membranes, DNA damage caused by ROS, and oxidative stress. It enhances the antioxidant defense system by modulating antioxidant enzymes through down-regulation of extracellular signal-regulated kinase (ERK) activated by ROS. In addition, it has a role in increasing the activity of antioxidant enzymes such as SOD, HO-1, CAT, GSH-px, which are involved in the antioxidant defense system, and phase II detoxifying enzymes, and inducing the glutathione level, which is responsible for maintaining the cellular redox balance (Leonard, 2003; Truong, 2018; Liu, 2014). Due to its antioxidant properties, resveratrol prevents diseases such as cardiovascular diseases, liver diseases, obesity, diabetes, and Alzheimer's, as well as exhibiting antitumor activity against many tumor cells, myeloid lymphoid cancer cells, skin, breast, stomach, cervix, ovary, colon, prostate, pancreas, liver, including thyroid carcinoma cells and is considered a potential candidate for the prevention and treatment of these types of cancer. It was confirmed by many in vitro and in vivo studies that resveratrol can inhibit stages of carcinogenesis such as initiation, progression, and progression (Meng, 2020; Vervandier-Fasseur, 2019; Tome-Carneiro, 2013; Harikumar, 2010). Resveratrol affects various cancer stages from initiation and progression to progression by affecting various signal transduction pathways that regulate cell cycle, cell growth and division, autophagy, inflammation, apoptosis, metastasis and angiogenesis (Singh, 2018). It was shown that Resveratrol, together with cyclin-dependent kinases (CDKs), changes the balance of cyclins, causing cell cycle inhibition in G0/G1 phase in different cancer cells by inhibition of cyclin D1/CDK4, cell cycle arrest in G2/M and S phases and cyclin A and E levels, increasing the activation of the p53-dependent pathway. It induces apoptosis by inhibiting the phosphorylation of Akt in ovarian, breast, uterus, prostate and multiple myeloma cells. Resveratrol inhibits the expression of angiogenesis markers such as MMP (specifically MMP-9), EGFR, VEGF, or FGF-2 (Ferry-Dumazet, 2002; Filippi-Chiela, 2016; Ko, 2017).

Resveratrol therapy in breast cancer MDA-MB231 and HepG2 cells reduced MMP-9 activity or inhibited its expression. Again, resveratrol showed proliferation inhibitory and apoptosis-inducing effects by activating caspase-3 and caspase-9, increasing the Bax/Bcl-2 ratio, upregulating TIMP-1 protein expression, and inducing p53 expression in HepG2 cells (Meng, 2020; Weng, 2010; Ou, 2014). In human skin cancer A431 cells, resveratrol was shown to inhibit CDK2, CDK4 and CDK6 activities and/or expression, downregulate cyclin D1, cyclin D2 and cyclin E expression, and upregulate p21 expression, thereby reducing the growth of these cells. Administration of resveratrol to breast cancer MCF-7 and human prostate cancer DU-145 cells also suppressed the proliferation of these cells by modulating the expression of CDK4 and cyclin D1, which is associated with the induction of p21 and p53. Resveratrol induces death of tumor cells by modifying proteins of the Bcl-2 family, modulating various signal transduction pathways through regulation of Fas and Fas-ligand (FasL) levels. Resveratrol triggers apoptosis dependent on Fas signaling in HL-60 cells by increasing FasL expression. (Ko, 2017; Delmas, 2011). During DENA-induced rat liver carcinogenesis, resveratrol was shown to suppress elevated HSP70, COX-2 and NF-kappaB levels, increase the expression of Nfr2, a transcription factor involved in the expression of antioxidant genes, and inhibit the formation of hepatocyte nodules, possibly through anti-inflammatory effects. In another study it was shown that the DENA-induced hepatic TNF-α, IL-1β, and IL-6 levels and expression of resveratrol can be reversed (Bishayee, 2010; Mbimba,

2012). Resveratrol was shown to increase both the expression and activity of the carcinogen detoxifying phase-II enzyme NAD(P) H:quinone oxidoreductase-1 in human leukemia K562 cells and mouse liver cancer Hepa 1c1c7 cells, and the metabolic enzyme quinone reductase, the carcinogen detoxifying phase-II enzyme. Resveratrol suppresses the activation of NF-kB, which regulates numerous genes that promote inflammation, proliferation, tumorigenesis, and protect against apoptotic cell death. And again it suppresses the activation of STAT-3 activators, the important element that supports the proliferation, survival, invasion, angiogenesis and metastasis of tumor cells. The aberrant signaling of resveratrol in malignant cells of two centers (STAT3 or NF-κB) linking tumorigenesis and inflammation is considered a promising target for cancer treatments (Hoesel, 2013; Ko, 2017; Johnston, 2011). It was shown that addition of resveratrol to drinking water delayed the growth of spontaneous mammary tumors in HER-2/neu transgenic mice, whereas in HBx transgenic mice, spontaneously resveratrol significantly reduced the incidence of hepatocellular carcinoma, increased the delay of tumor formation, inhibits intracellular ROS, in a transgenic adenocarcinoma mouse prostate model, resveratrol was shown to significantly reduce the incidence of prostate adenocarcinoma (Provinciali, 2005; Lin, 2012). In DMBA-TPA mouse-skin carcinogenesis model, resveratrol was reported that resveratrol application increases SOD, GSH-px, CAT activities and glutathione (GSH) levels, decreases H_2O_2 and lipid peroxidation in the skin, prevents the development of mouse skin tumors, and induces cytochrome c release (Kapadia, 2002; Aziz 2005). Resveratrol influences tumor suppressor activities in SW480 colon cancer cells and increases miR-663 levels, which target TGFβ1 transcripts by reducing the levels of several oncogenic miRNAs that target genes encoding effectors of the TGFβ signaling pathway. While upregulating several components of the TGFß signaling pathway, it reduced the transcriptional activity of SMADs (Tili, 2010). In two different clinical studies, in which 50 mg twice daily for 12 weeks and once daily resveratrol supplementation for 12 weeks, DNA methylation of the tumor suppressor gene Ras association domain-containing protein 1 (RASSF1A) was decreased in the breasts of women at higher risk of breast cancer, sex steroid hormone binding globulin (SHBG) concentrations were increased (Ko, 2017). Increased expression of positive G1/S and G2/M regulators, reduction of Bcl-2 and Bcl-XL, overexpression of Bax and activation of caspase-9 were detected in the MCF-7 cell line exposed to resveratrol (Nguyen, 2008; Sinha, 2016). It was reported that resveratrol induces cell shrinkage and apoptosis through activation of caspase-3 and -9 in human cervical carcinoma HeLa cells, and shows apoptotic and anti-proliferative effects as a result of upregulation of proapoptotic B-cell lymphoma expression.

CONCLUSION

Although cancer information and cancer treatment experience have progressed very well, unfortunately, the prevalence and mortality of the disease still continues to increase. Eating habits and lifestyle are an easy, fast and low-budget practical way to protect against cancer. Despite years of research, further studies are needed for the use of antioxidants in cancer prevention and treatment. As described above, in vitro and in vivo studies have shown that antioxidants such as CAPE, Quercetin, Resveratrol are important in cancer prevention, cancer treatment, and modulation of metastatic spread. High levels of ROS, which play a role in the etiology of cancer, promote the tumor, and antioxidants, which purify this ROS, may be a promising therapeutic strategy in anticancer.

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Chapter 19
A Natural Bioactive Compound Lycopene and Its Role on Cancer Related to Oxidative Stress

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ABSTRACT

The inequality between the production of free radicals and reactive oxygen species, and their elimination by protective mechanisms, is defined as oxidative stress, which destroys cell components by creating various forms of free radicals that influence the pathogenesis of many diseases, such as cancer. Natural preservatives such as phytochemicals inhibit the production of free radicals and maintain oxidative balance. Lycopene, which has the high antioxidant ability, is one of these phytochemicals that reduces oxidative stress markers. Studies show a connection between a lycopene-rich diet in the prevention of oxidative stress harm. Lycopene is believed to minimize the risk of cardiovascular disease, cancer, metabolic syndrome, and obesity. In this chapter, the biochemical, structural, chemical, biological, and oxidative stress mechanisms of lycopene are evaluated, and the role of lycopene on cancer is discussed.

INTRODUCTION

The balance between pro-oxidants and antioxidants is extremely important for maintaining vital cellular and biochemical functions. Changing the balance in favor of the pro-oxidant over the antioxidant capac-

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ity is defined as oxidative stress and can lead to oxidative damage (Kohen & Nyska, 2002). Biological systems contain specific mechanisms that keep this stress under control. Oxidative stress may occur in cases where control mechanisms are insufficient (Serafini & Del Rio,2004). The cell and the entire organism have developed indirect and direct activities of defense systems to guard against reactive metabolites because of constant exposure to various types of oxidative stress from different sources. These defense systems are repair and prevention mechanisms, physical defenses, and antioxidant defenses (Kohen & Nyska, 2002).

Antioxidants can protect cells by converting reactive oxygen species (ROS) to non-radical species (depending on the antioxidant), stopping the auto-oxidative chain reaction started by ROS, and lowering localized oxygen concentrations. Exogenous antioxidants contained in widely ingested fruits, vegetables, drinks, cereals, and other dietary products, such as ascorbic acid (Vitamin C), -tocopherol (Vitamin E), carotenoids, and polyphenols, may help to promote the antioxidative defense (Lourenço et al., 2019).

Carotenoids primarily exhibit antioxidant activity through their conjugated double-bonded structures that de-localize unpaired electrons and provide substantial tissue protection against oxidative damage (Flora, 2009). Carotenoids are antioxidants with significant protective effects against oxidative damage in tissue. It has provided insights into the health effects of lycopene to minimize the risks and complications associated with various chronic diseases, such as cardiovascular diseases (CVD), obesity, type 2 diabetes, cancer, and neurodegenerative diseases, that are based on recent cognitive studies. These chronic diseases are mainly connected with systemic and low-grade chronic inflammation caused by oxidative stress.

Lycopene, one of the important carotenoids with its strong antioxidant capacity, is one of the most significant non-enzymatic antioxidant agents that are not synthesized in the human body but obtained from consumed foods. Lycopene is a major component of the carotenoids found in serum. Lycopene levels have also been shown to be high in the testes, adrenal glands, and prostate (Rao & Agarwal, 1999). Lycopene can potentially minimize elevated levels of pro-inflammatory mediators (e.g., pro-inflammatory cytokines IL-8, IL-6, and IL-1). It prevents NF-kB activation by modulating oxidative stress due to its strong antioxidant properties. Lycopene appears to protect lipoproteins and vascular cells from oxidation *in vitro*, although there is no evidence *in vivo*. Several studies are reporting consuming high content lycopene food lowers the risk of cardiovascular disease and cancer. In several clinical studies, lycopene has been found as a natural origin agent to reduce oxidative stress, especially by preventing LDL oxidation (Chen et al.,2019; Saini et al., 2020). Lycopene is the strongest antioxidant among carotenoids since it has 11 conjugated double bonds. Therefore, lycopene protects DNA, lipids, and proteins from oxidative damage. Cell cycle arrest, immune function regulation, and activation of apoptotic cell death are all possible lycopene mechanisms. Lycopene also reduces phosphorylation of the kinase (ERK) regulated by extracellular signaling through inhibition of ROS production, thereby inhibiting cancer cell growth (Kim & Kim, 2015).

In this chapter, firstly free radicals and oxidative stress will be briefly discussed. In the next part a summary of lycopene, its main properties, functions, and oxidative stress-related studies will be presented. Lastly, lycopene's therapeutic effect of cancer will be discussed in detail.

BACKGROUND

Free Radicals, Reactive Oxygen Species and Oxidative Stress

Free radicals, which are unstable and highly reactive, can be defined as any molecular species that can exist independently, containing an unpaired electron in an atomic orbit. They can give an electron to other molecules or take an electron from them, so they act as an oxidant or reductant (Lobo et al., 2010). It is accepted that free radicals are basically formed by the homolytic division of a covalently bonded normal molecule with one of the common electrons in each part, the addition of a single electron to a normal molecule and the loss of an electron in a normal molecule (Ozcan et al., 2015).

ROS and reactive nitrogen species (RNS) are reactive radical and non-radical oxygen and nitrogen derivatives, respectively. All aerobic cells create reactive oxygen and nitrogen species (RONS), which play a key role in aging and age-related illnesses (Liguori et al., 2018). Both endogenous and exogenous sources of RONS are known. Mitochondrial respiration, cytochrome P450 metabolism, peroxisomes, and inflammatory cell activities are all examples of endogenous sources. Environmental factors such as radiation, chlorinated chemicals, metal ions, air-polluting gases, and cigarette smoke are examples of exogenous sources (Inoue et al., 2003; Kargın & Fidancı, 1997). Mitochondrial dysfunction and ROS formation play a role in the formation of cytotoxicity. Mitochondria are involved in both cell health and cell death. At multiple levels, mitochondria have been proven to be engaged in active control of cell death processes (Eskandri et al., 2013). Exogenous toxicants that can damage cells induce cell toxicity, especially when the toxicant can cause cell death and significant organ malfunction. Overproduction of nitric oxide (NO), ROS, and oxidative stress may be caused by toxicants. Oxidative stress has also been linked to mitochondrion dysfunction, particularly in neuronal cells. Some toxins can cause mitochondrial dysfunction, which can lead to cell death (Zhang, 2018).

The antioxidant protection system will neutralize the negative effects of RONS created by various endogenous and exogenous processes. An imbalance between RONS activity and the antioxidant protection mechanism causes oxidative stress. Exogenous and endogenous RONS induce oxidative modifications of all cellular macromolecules (carbohydrates, lipids, proteins, and DNA), which can be used as oxidative stress markers (Liguori et al., 2018). Age-related illnesses such as arthritis, diabetes, hypertension, cancer, atherosclerosis, vascular diseases, obesity, osteoporosis, and metabolic syndromes are all linked to oxidative stress (Tan et al., 2018). ROS trigger oxidative stress, which is characterized as a breakdown in the pro-oxidant-antioxidant balance that promotes oxidation. It is also linked to the occurrence of a variety of diseases. The overall oxidative/reducing strength of a given sample (e.g. blood or urine) or the susceptibility of different oxidizable components to ex vivo peroxidation are used to determine the oxidative state (Pizzino et al., 2017). ROS are produced because of normal intracellular metabolism in mitochondria and peroxisomes, also other enzyme systems containing NADPH oxidase. ROS formation may also be triggered by exogenous sources such as ultraviolet light, ionizing radiation, environmental contaminants, cooking, industrial solvents, inflammatory cytokines, and chemotherapeutics (Liguori et al., 2018).

As active reactive oxygen species in oxidative stress, free radicals such as superoxide ($O2^{-}$), hydroxyl (OH), peroxyl (RO_2), hydroperoxyl (HRO_2^{-}), and non-radical species such as hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl) may be seen. Nitric oxide (NO), nitrogen dioxide (NO_2^{-}), and non-radicals such as peroxynitrite ($ONOO^{-}$), nitrous oxide (HNO_2), and alkyl peroxy nitrate are examples of free radicals. By radical chain reactions, the formation of free oxygen radicals (SOR) or reactive nitrogen species

contributes to the creation of other products (Johansen et al., 2005). In the production of ROS, the Fenton and Haber-Weiss reactions are essential. Fenton's reaction is defined as the reduction of hydrogen peroxide (H_2O_2) with iron (Fe^{2+}) or other transition elements. Ferric iron (Fe^{3+}) and hydroxyl radical (OH.) are formed in this reaction. The hydroxyl radical (OH) then reacts H_2O_2 to produce superoxide (O_2^-). The hydroxyl radical (OH) and the hydroxyl anion (OH^-) form when the superoxide radical reacts with H_2O_2 again. This part of the reaction is known as the "Haber-Weiss Reaction" (Das et al., 2015). In addition to causing oxidative stress, excessive accumulation of ROS in the cell jeopardizes cell membrane integrity, membrane potential, and respiratory chain with serious destructive effects on cellular components and causes its effect on mitochondria (Salehi et al., 2018). ROS can cause oxidative damage by causing various modifications in DNA such as base changes, mutation, translocation, and cross-linking with proteins. The role of oxidative DNA damage in aging, cardiovascular, neurodegenerative, autoimmune diseases, and carcinogenesis, is well understood (Bennet, 2001). Lipids are the structures most sensitive to the toxic effects of reactive oxygen products among biological structures. Reactive oxygen species can inactivate membrane-bound receptors and enzymes by inducing lipid peroxidation in the form of chain reaction, with deterioration in cell membrane fluidity and changes in permeability (Girotti, 1985; Halliwell & Gutteridge, 2015; Kohen & Nyska, 2002). The amino acid composition in proteins is a factor that determines how it will be affected by free radical damage. Proteins with cysteine and methionine residues are more susceptible to oxidation. Reactive oxygen species (ROS) can cause the variation of the electrical charge of proteins, modification of certain amino acids, and fragmentation of the peptide chain (Kelly, & Mudway, 2003). In the evaluation of oxidative stress, antioxidant enzyme activities, such as superoxide dismutase (SOD), catalase, glutathione reductase, total antioxidant capacities (TAOC), lipid oxidation products, such as malondialdehyde (MDA), thiobarbituric acid, protein oxidation products, such as nitrosamines and carbonyl groups, and biomarkers such as reduced/oxidized glutathione ratio can be used (Birben et al., 2012; Buettner & Schafer, 2000; Nordberg, & Arnér, 2001).

Antioxidant protection systems, especially enzymatic scavengers like SOD, catalase, glutathione peroxidase, and peroxiredoxin, help to counteract the effects of ROS (Noh & Ha, 2011). The cleaning, suppression, repair, and chain-breaking effects of endogenous and exogenous antioxidants are of great importance in the inhibition of oxidative damage caused by free radicals (Valko et al., 2007).

LYCOPENE

Plant antioxidants can be divided into three categories: phenolic chemicals, vitamins, and carotenoids. Vanillin, gallic acid, tannins, and flavonoids are significant plant chemicals with antioxidant activity, but they also have antibacterial and antifungal properties. Vitamins E and C are the most important in terms of vitamins. Fruits and vegetables contain many carotenoids. The primary carotenoids with antioxidant activity include α-carotene, β-carotene, lycopene, and lutein. They have the potential to be employed as food colorants in addition to their antioxidant properties (Lourenço et al., 2019).

Lycopene is a lipophilic carotenoid found especially rich in red fruits and vegetables such as tomatoes, asparagus, pink grapefruit, guava, watermelon, peach, papaya, and red carrot (Balić & Mokos, 2019; Ahmad, 2019). Lycopene can be produced naturally and synthetically. Natural methods to obtain lycopene include microbial fermentation. Lycopene is used as a food color in the food production sector (Martínez-Cámara et al., 2018). Natural lycopene is synthesized by *Blakeslea trispora* in plants for industrial use (Papaioannou et al., 2016). Lycopene's molecular formula is $C_{40}H_{56}$. It has linear hydrocarbons.

Table 1. Physical and chemical properties of lycopene (Arballo et al., 2021; Clinton, 1998; Gutiérrez et al., 2007; Shi & Le Maguer, 2000)

Molecular formula:	$C_{40}H_{56}$
Molecular weight:	536.85 Da
Melting Point:	172–175 ° C
Chemical Structure:	It is an unsaturated acyclic carotenoid with 11 linear conjugated and two non-conjugated double bonds. There is no P ionone ring. It has no provitamin A activity. It is found in nature in a state of trans. The presence of conjugated double bonds renders lycopene susceptible to isomerization by heat, thus leading to the formation of 9-cis, 13-cis or 15-cis lycopene isomers. The number of isomers is 72 in nature due to steric hindrance.
Crystal form:	It is in the form of long red needles in a mixture of carbon disulfide and ethanol.
Powder form color:	It is dark reddish brown.
Resolution:	It is soluble in chloroform, hexane, disulfide, acetone, benzene, etc. It is insoluble in water, ethanol, methanol
Sensitivity:	It is sensitive to light, oxygen, high temperatures and acids.

11 conjugated and two unconjugated bonds found in lycopene. When lycopene exposes to light, heat, or chemicals, it can transform into 5-cis, 9-cis, 13-isomerization. While lycopene is insoluble in water due to its acyclic structure, it can easily be soluble in organic solvents such as methylene, benzene, and chloroform (Grabowska et al., 2019). During the digestion of lycopene, there is a loss of ≈20%. Dietary iron ($FeSO_4$) significantly reduces lycopene absorption in the stomach and intestines (Story et al., 2010). The physical and chemical properties of lycopene are in Table 1.

Tomato foods are the main sources of daily carotenoids and lycopene consumption. Approximately 85% of the total lycopene in the human diet is thought to come from tomatoes (Chaudhary et al., 2018). Tomato and tomato derivatives, such as raw tomatoes (9.2 mg), tomato paste (55.4 mg), tomato sauce (18 mg), and tomato juice (10.8 mg), have high lycopene concentrations (mg/100 g). Some studies have found correlation between serum lycopene levels and tomato consumption (Salehi et al., 2019). For example, plasma or serum lycopene concentration may vary between 60 ng/ml and 600 ng/ml (Wiese et al., 2019). The consumption of foods rich in lycopene during the breastfeeding period increases the lycopene. Lycopene amount is low in breast milk (Duan, 2019). Epidemiological studies suggest that lycopene-rich diets may reduce the risk of cardiovascular disease, cancer, metabolic syndrome, and obesity by affecting inflammation (Thives et al., 2017; Fenni et al., 2017).

Because of its conjugated double bonds, lycopene has the potential to be an effective antioxidant. According to epidemiological studies, eating foods high in lycopene lowers the risk of cardiovascular disease and cancer. Several clinical trials have shown that lycopene decreases oxidative stress, specifically by blocking LDL oxidation (Chen et al., 2013). While cellular and molecular studies indicate that lycopene is one of the most effective antioxidants, it has also been stated that lycopene protects essential biomolecules such as DNA, lipids and proteins thereby preventing cancer and atherogenesis (LDLs). Owing to its high number of conjugated double bonds, lycopene has a great singlet oxygen quenching ability than β-carotene and α–tocopherol (Basu, & Imrhan, 2007). The molecular and physical structures

of lycopene, as well as its position of action within cells, its capacity to react to other antioxidants, the concentration and partial pressure of oxygen, all influence its reactivity.

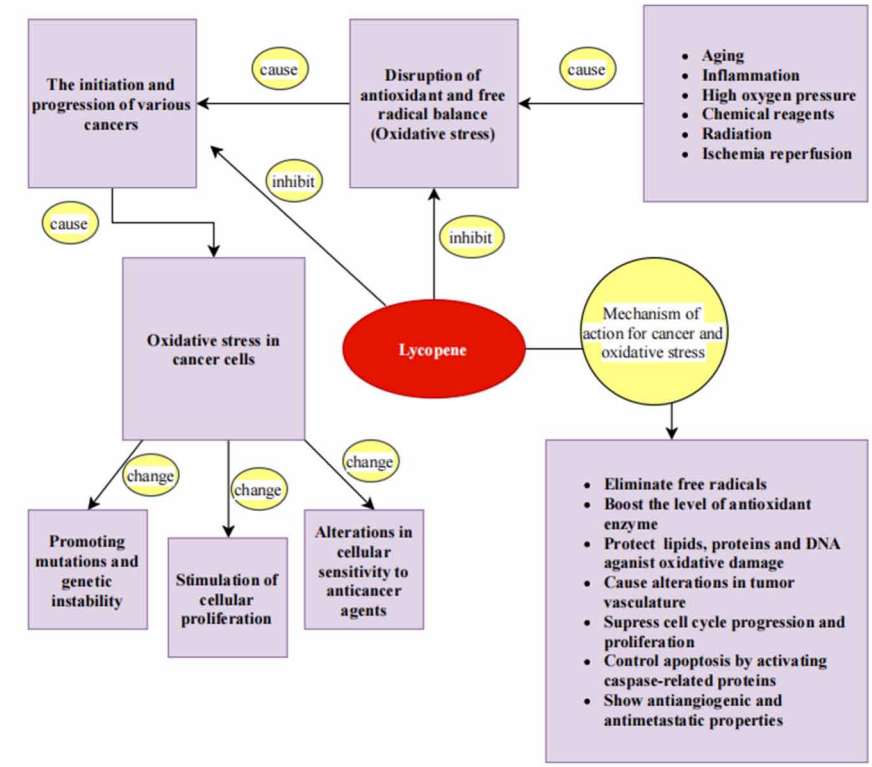
Lycopene acts biologically like singlet oxygen (1O2) and peroxyl radical scavenger (LOO •). Lycopene's antioxidant properties are primarily linked with a pre-conjugated double bond in which electrons are delocalized over the total length of the polyene chain, allowing chemical reactions to take place with molecules including unpaired electrons (Przybylska, 2020). Lycopene (5 μM and 10 μM) restrained iron-catalyzed lipid peroxidation and nitric oxide formation by roughly 31 and 61 percent, respectively, in an analysis to investigate the preventive impact of lycopene on ischemic brain damage in rat brain homogenates (Hsiao et al., 2004). According to the results of a study, lycopene has a beneficial impact on lowering malondialdehyde (MDA) levels and raising glutathione (GSH) levels in postmenopausal women with coronary artery illness (Misra et al., 2006). The antioxidant enzymes are considerably restored by lycopene by lowering GSH levels, according to a different study. It was also found that lipid peroxide MDA levels were lower in hypertensive patients (Bose & Agrawal, 2007). Nitric oxide production causes many reactive species, including peroxynitrite (ONOO-), which can cause tissue damage. In another study, lycopene was found to inhibit stress-induced DNA damage of 3-morpholinosydnonimine or SIN-1 in Chinese hamsters at concentrations ranging from 0.31 to 10 μM. It has been suggested that lycopene's protective role is attributable to its inhibition of intracellular free radical species (Jamshidzadeh et al., 2008). Studies have shown that lycopene improves endothelial function by increasing the bioavailability of nitric oxide (NO), enhancing endothelium-dependent vasodilation, reducing protein, lipids, DNA, and mitochondrial damage, and increasing its antioxidant potential.

The metabolism of lycopene is just beginning to be understood today, and some studies suggest that lycopene metabolites may be responsible for the bioactivity associated with the parent compound. Lycopene's metabolism includes both chemical and enzymatic oxidation (Cichon et al., 2018). Polymorphic single nucleotide change has been discovered in watermelons with high lycopene content (Subburaj et al., 2019). Besides, the activity of the gene named MaLCYB1.1 to convert lycopene-to-carotene is temperature-sensitive (Fu et al., 2019).

It is well understood that oxidative stress plays a key role in cardiovascular disease. However, a decline in serum lycopene levels has been identified as one of the most significant factors in the development of cardiovascular diseases. Daily lycopene supplementation has been shown to raise serum lycopene concentration by decreasing oxidative stress markers, as well as improving antioxidant status. Lycopene also protects the skin against aging due to its antioxidative capacity, anti-inflammatory effects, effect on gene expression, and its ability to protect against lipid peroxidation (Doyle, 2020). The general mechanism of action of lycopene in preventing the formation processes of oxidative stress and cancer disease is summarized in Figure 1.

Supplementing with capsules containing lycopene-rich troponin C (TNC) and lutein for humans resulted in a substantial decrease in UV-induced mRNA expression of HO-1, MMP-1, and ICAM-1 (Darwin et al., 2011). In another research, lycopene was found to protect human SH-SY5Y neuroblastoma cells from hydrogen peroxide-induced death by inhibiting apoptotic pathways linked to oxidative stress and mitochondria. Lycopene was found to have a very powerful neuroprotective effect against mitochondrial damage as well as oxidative stress (Feng, 2016). The influence of lycopene on antioxidant status and homocysteine (HCY) levels in patients on dialysis undergoing intravenous iron treatment was examined in a study. When compared to the control group, the treatment group had higher SOD and GSH-px levels and lower MDA levels. They found that supplementing with lycopene for eight weeks decreased oxidative stress in hemodialysis patients undergoing intravenous iron therapy (Xu et al., 2019). One research

Figure 1. General mechanism of action of lycopene in preventing the formation processes of oxidative stress and cancer disease



investigated how lycopene affected caspase-dependent apoptosis in a PC12 cell line treated with high-dose glucose (HG). It has been reported that different lycopene doses reduced oxidative DNA damage, particularly in HG-treated groups (Bazyel et al., 2019). Previously, it was investigated whether lycopene attenuates oxidative damage and underlying molecular mechanisms in bovine mammary epithelial cells (bMEC) induced by hydrogen peroxide (H_2O_2). They reported that it decreased the expression of IL-6, IL-1, and the rate of apoptosis (Sun et al., 2019). Besides, lycopene positively affects cardiac hypertrophy by suppressing ROS-dependent mechanisms (Zeng et al., 2019). Researchers reported that 5 mg/kg of lycopene (its equivalent in humans, 0.79 mg/kg and above) given to rats with type 2 diabetes per day could prevent the progression of type 2 diabetes (Zheng et al., 2019). Researchers determined in their study that lycopene reduced aflatoxin-induced erythrocyte oxidative stress by decreasing the H_2O_2 and MDA content and increasing SOD, CAT activities (Zhang et al., 2020). Oxidative stress is a significant contributor to the development of neurodegenerative disorders such as Alzheimer's. In a study examining the mechanism of preventing Alzheimer's by lycopene, it was found that Lycopene prevents M146L cells from oxidative stress and apoptosis by inhibiting β-secretase (BACE) and stimulating the PI3K/Nrf2 pathway (Fang et al., 2020).

Lycopene has been found to enhance biological activities, like Posttraumatic Stress Disorder (PTSD) in mice and reduces the symptoms of oxidative stress in the brain. They conclude that lycopene's anti-PTSD effects are due to its anti-neuroinflammation and anti-oxidative stress properties (Li et al., 2021).

Lycopene has been shown to suppress ROS formation in pancreatic cells, thus inhibiting EtOH/POA-induced mitochondrial damage and IL-6 expression (Lee et al., 2021).

LYCOPENE'S THERAPEUTIC EFFECT OF CANCER

Several studies have been performed to show the effects of lycopene on cancer, but they are preliminary and therefore need more investigation in this regard. Factors, such as the differentiation of the source of lycopene used in the studies, various dissolution techniques, the amount of concentration, and the upper limit may cause differentiation of the results. Some studies show an association between lycopene therapy and low cancer incidence and low insulin-like growth factor-1 concentration. In a study conducted with 5 different cancer cells (breast cancer, prostate, uterus), lycopene has been shown to inhibit the proliferation and growth of monolayer cultures (Aydemir et al., 2013; Holzapfel et al., 2016).

In another study, it was observed that lycopene provides the translocation of the transcription factor Nrf2 (nuclear factor erythroid 2- associated factor 2) by activating antioxidant enzymes. In addition, lycopene increased the expression of the autophagy protein p62. This led to the breakdown of Keap1 (Kelch ECH-associated protein 1), known as the main protein that locks Nrf2 in the cytoplasm. As a result, the mechanism of lycopene on cancer cells has been demonstrated by linking Nrf2 signaling pathways (Wang et al., 2020). Examining the effects of lycopene on the nuclear factor kappa B (NF-κB) pathway in prostate and breast cancer cells resulted inhibition of cell growth and suppress nuclear translocation by 25% at concentrations ≥1.25 μM (Assar et al., 2016). There are also studies showing the cancer preventive effect of lycopene through COX-2 and arachidonic acid pathways (Chen et al., 2020).

Levels of inflammatory factors, including IL-1, IL6, IL8, and tumor necrosis factor-α (TNF-α) in lycopene-treated cells of rats were also reduced by lycopene treatment (Jiang et al., 2018). In a study examining the relationship between lycopene and tomato sauce consumption, defined by the ERG protein expression subtype, prostate cancer risk of 46,719 men was studied for 23 years. A relationship has been found between increased consumption of tomato sauce and decreased risk of prostate cancer. The prostate cancers that contain TMPRSS2 may be etiologically different from fusion-negative cancers of ERG and tomato sauce consumption may influence TMPRSS2: ERG-positive prostate cancer (Graff et al., 2016).

In a study on breast cancer cells, the role of apo-8,6'-carotenoid in the induction of apoptosis has been demonstrated for the first time. These results show that lycopene oxidation derivatives or metabolites have a significant role in inhibiting the growth of cancer cells. Researching oxidized carotenoid products will benefit cancer research (Arathi et al., 2018).

Lycopene-loaded lipidic nano-structured particles are more effective in preventing apoptosis and cytotoxicity in breast cancer (Jain et al., 2017). According to a study conducted in China, it was found that lycopene consumption is not associated with the prevention of breast cancer (Wan et al., 2014). In a study that first demonstrated the effects of lycopene in individuals with oral cancer, lycopene inhibits the proliferation, migration, apoptosis, and xenograft tumor growth of oral cancer cells in a dose-dependent manner (Wang et al., 2020).

Lycopene contributes to the oxidative balance mechanism, helps preserve healthy cells and may benefit the treatment of colon cancer and rectal cancer (Perše, 2013). Lycopene inhibits the expression of NF-κB target genes by lowering mitochondrial ROS levels in pancreatic cancer cells. The results demonstrated that lycopene supplementation can lower the risk of pancreatic cancer (Jeong, 2019).

Lycopene, which has a variety of biological activities, induces apoptosis in gastric cancer cells by lowering ROS levels and blocking β-catenin nuclear translocation (Kim et al., 2019).

Carotenoid cleavage oxygenases (BCOs) and lycopene produce lycopene metabolites that are effective functional products on treatment of non-alcoholic fatty liver disease (NAFLD) dependent on obesity. Studies show that lycopene and lycopene metabolites (apolycopenoids) may have protective effects against complications associated with obesity, including inflammation and tumorigenesis (Ip & Wang, 2013). In addition, 0.1-5 μM lycopene prevents liver adenocarcinoma (SK-Hep-1) and NOX activity (Imran et. Al, 2020), increased 8-oxoguanine DNA glycosylase (OGG1) expression and is effective in preventing oxidative stress related to smoking (Cheng et al., 2020).

CONCLUSION

One of the primary causes of various diseases is the generation of free radicals and the loss of free radical scavengers. It is due to the accumulation of ROS that includes inflammation and irregular lipid metabolism, which is one of the most serious health issues associated with ageing.

Lycopene, a powerful antioxidant, can show its beneficial effects on various diseases. Because of its capacity to neutralize free radicals and reduce oxidative stress, lycopene is thought to provide great protection against several diseases, such as cardiovascular disease, inflammatory diseases and especially cancer. Lycopene is also important in the treatment of aging and chronic health problems due to its different biological activities, especially its anti-inflammatory and antioxidant effects. Lycopene plays an important biological function in preventing DNA damage caused by oxidative stress by quenching oxygen and inhibiting mutations that can lead to chronic diseases. Due to the conjugated double bonds in its structure, lycopene is one of the most important carotenoids which demonstrates free radical scavenging effect and regulates cell formation, immune response, and the control of detoxifying enzymes. Various *in vitro*, animal, and human studies have shown that lycopene prevents oxidative stress by demonstrating its antioxidant activity in a variety of ways, including activation of cytoprotective enzymes by destroying ROS, and inhibition of various signaling pathways.

Lycopene has also known as an effective antioxidant for cancer, the illnesses that has proven to be difficult to cure around the world. During metastasis, cancer cells can divide indefinitely and spread to different areas of the body. Seeking new therapeutic agents for the molecular treatment of cancer requires detecting changes in the signal transduction system that plays a role in cancer pathogenesis. Previous studies have shown that lycopene is a powerful antioxidant that protects cells from free radical damage, strengthens cell bonds, improves cell metabolism, and has critical regulatory effects on mutation, carcinoma formation, cell differentiation, and growth. Lycopene inhibits cancer cell growth and differentiation by inducing the synthesis of cell cycle regulatory proteins, inactivates interleukin (IL-6) and androgens, inhibits the 5-lipoxygenase-enzyme, enhances the immune system, prevents lipid peroxidation, and increases the activity of cox enzyme inhibitors.

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KEY TERMS AND DEFINITIONS

Antioxidant: Substances that may protect your cells against free radicals, which may play a role in heart disease, cancer, and other diseases.

Apoptosis: The death of cells which occurs as a normal and controlled part of an organism's growth or development.

Cancer: A disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.

Cell Cycle: The ordered sequence of events that occur in a cell in preparation for cell division.

Flavonoids: Any of a large class of plant pigments having a structure based on or similar to that of flavone.

Free Radicals: An uncharged molecule (typically highly reactive and short-lived) having an unpaired valency electron.

Oxygen Reactive Species: A phrase used to describe a number of reactive molecules and free radicals derived from molecular oxygen.

Section 4

Novel Approaches of Natural Agents as Cancer Therapeutics

Chapter 20
Nanotechnology Applications in Breast Cancer

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ABSTRACT

Breast cancer is the most common malignant disease in women worldwide. Despite much technological progress, the current clinical therapy's lack of specificity leads to reduced therapeutic efficiency and serious systemic side effects. In recent years, nanotechnology applications for cancer treatments have attracted a lot of attention because of their advantages in tumor targeting, prolonged blood circulation time, and enhanced accumulation of drugs in tumors. Many liposomal and polymeric-based formulations have been developed to treat breast cancer and showed significantly higher efficiency than free drugs in clinical trials. The versatility of nanoparticles allows for the delivery of multiple active agents with the ability to target various types of cancer. Nanotechnology is a promising field that is expected to introduce new strategies to positively impact the survival rates and quality of life of breast cancer patients. This chapter presents the advantages and disadvantages of nanotechnology applications in breast cancer.

1. INTRODUCTION

The term "nanotechnology" is a concept that has only emerged in the last decade with the prefix "nano" cited from the Greek word "nanos", indicating that something is dwarf sized. Therefore, the term "nanotechnology" refers to a technology that uses very small particles invisible to the naked eye. Before the 21st century, nanotechnology had not yet been globally defined, but the applications of nanotechnology were already used (Sharma, Bhatia et al. 2019). Breast cancer has been recognized as one of the most fatal

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diseases that greatly threaten the quality of life of women around the world. Nowadays, cancer treatments have been performed based on clinical and pathologic staging that is determined using morphologic diagnostic tools, such as radiological and histopathological examinations. The most common cancer treatments are used such as chemotherapy, radiation and surgery (Misra, Acharya et al. 2010). Conventional chemotherapeutic drugs are distributed non-specifically in the body and that leads to significant complications that represent a serious obstacle to effective anticancer therapy. In addition, multidrug resistance reduces the efficacy of cancer treatment. To overcome the lack of specificity of conventional chemotherapeutic drugs, several ligand-targeted therapies have been used, including immunotoxins, radio immunotherapeutics, and drug immunoconjugates, are being developed. Although these methods have shown promising efficacy compared with conventional chemotherapy drugs, limitations remain. In this regard, it has been attempted to utilize nanomaterials to develop platforms for the treatment of breast cancer (Wang, Wang et al. 2009). The beginning of the 21st century marked an increased interest in the emerging fields of nanotechnology. It has the potential to revolutionize cancer diagnosis and therapy. Its advantages have been found in multifunctional nanoparticle probes for molecular and cellular imaging, nanoparticle drugs for targeted therapy, and integrated nanodevices for early cancer detection and screening. These developments have opened potential opportunities in which cancer detection, diagnosis and therapy are tailored to each individual's molecular profile, and also for predictive oncology (Rocha, Chaves et al. 2017).

2. NANOTECHNOLOGY

2.1. Nanocarriers: Properties and Advantages

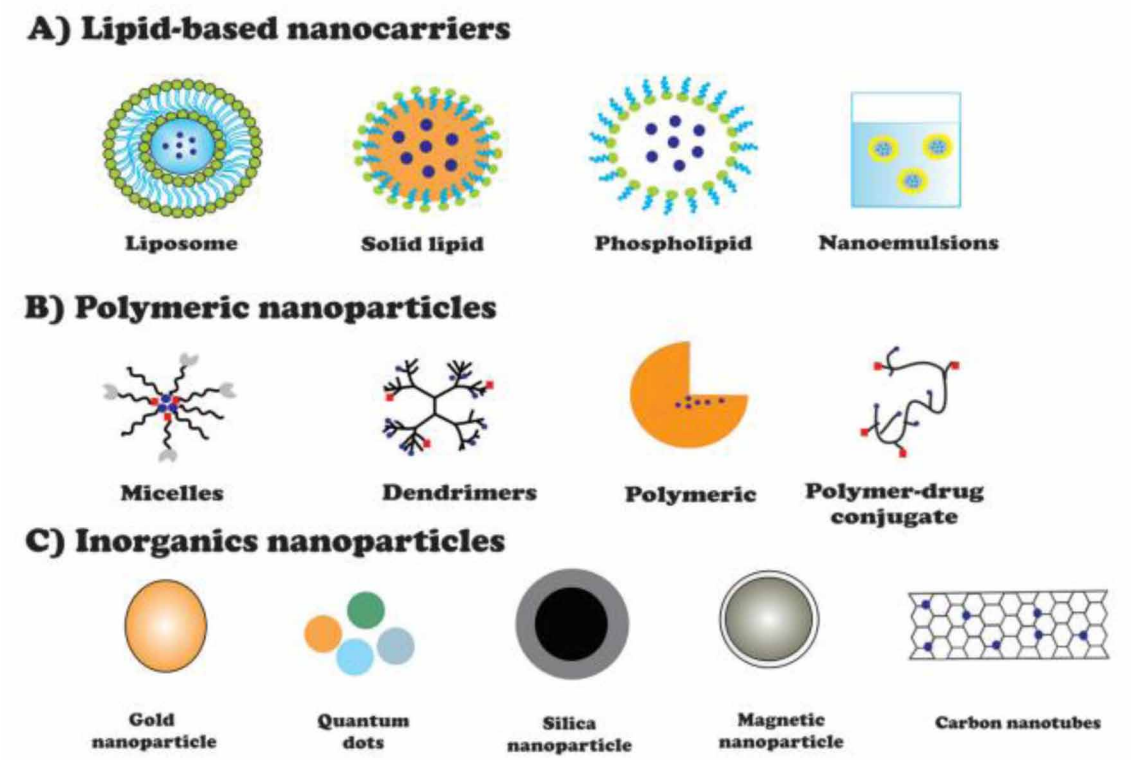
Nanocarriers are nanosized materials (diameter 1–100 nm) that can carry multiple drugs and/or imaging agents. Owing to their high surface-area-to-volume ratio, it is possible to achieve high ligand density on the surface for targeting purposes. Nanocarriers can also be used to increase local drug concentration by carrying the drug within and control-releasing it when bound to the targets (Peer, Karp et al. 2007).

Nanocarriers have several advantages over free drugs. They help improve drug efficacy through encapsulation of hydrophobic drugs within the core of the nanocarriers. They have the ability to protect the drug from premature degradation, inhibit premature interaction of drug with the biological environment, improve cellular penetration, control pharmacokinetic and drug tissue distribution profile, and enhance absorption of the drug in a given tissue (for instance tumor, due to their leaky constitution) (Rawat, Singh et al. 2006). Nanocarriers are made from polymers, lipids or phospholipids and inorganic compounds. These nanocarriers have been applied to diagnostics, drug delivery (radiation and chemotherapy) and molecular medicine (Torchilin 2007).

2.1.1. Liposome

Liposomes were the first nanocarriers that have been used successfully in the field of biology, biochemistry and medicine. Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are formed when thin lipid films or lipid cakes are hydrated and stacks of liquid crystalline bilayers become fluid and swell. During agitation, hydrated lipid sheets detach and self-associate

Figure 1. Schematic of different kinds of nanocarriers used for drug delivery. (A). Lipid-based nanocarriers (B). Polymeric nanoparticles (C). Inorganics particles [1]



to form vesicles, which prevent the interaction of water with the hydrocarbon core of the bilayer at the edges. Small unilamellar vesicles (SUVs) are surrounded by a single lipid layer (25—50 nm) whereas several lipid layers separated by an intermittent aqueous layer surround large unilamellar vesicles (LUV). Liposomes are characterized concerning composition, size, surface charge and method of preparation (Torchilin 2005). Liposomes can be surface modified by various strategies to endow them with multiple functionalities, including long systemic circulation, increased accumulation at the target tissue, increased cellular internalization and organelle-specific drug delivery. Liposomes play an important role in targeting tumor strategies including passive and active targeting. By exploiting the enhanced permeability and retention (EPR) effect of liposome particles that are smaller than 400nm in size, the drugs accumulate in the interstitial fluid of the tumors. The composition and charge on the surface of liposomes are other factors that influence passive targeting. For example, polyethylene glycol (PEG) is usually added to the surface of liposomes to reduce uptake by the macrophages of the mononuclear phagocytic system and prolong their circulation in the blood. Anionic or neutral liposomes escape from renal clearance. Liposomes can also be actively targeted by modifying the liposomal surface with various ligands that interact with overexpressed cancer cell surface receptors, or receptors and antigens present in the tumor microenvironment. The ligands utilized for tumor microenvironment targeting include folate, transferrin, antinucleosome antibodies, or antibodies against VEGF, VCAM, matrix metalloproteases and integrins (Danhier, Feron et al. 2010, Deshpande, Biswas et al. 2013, Khawar, Kim et al. 2015).

Many liposome-encapsulated formulations have been developed for doxorubicin and paclitaxel to improve effectiveness and reduce cardiotoxicity. Doxil® and DaunoXome® were the first clinically approved by the FDA for breast cancer treatment. Besides, many liposomal drugs are ongoing clinical trials such as ThermoDox®, EndoTAG-1®, LEP-ETU® (Bulbake, Doppalapudi et al. 2017). Thus, future work using liposomes as basic constructs for improved chemotherapeutics is very promising.

2.1.2. Polymeric nanoparticles

Polymeric nanoparticles based on biodegradable and biocompatible polymeric systems have largely influenced the controlled and targeted drug delivery concept. Polymeric nanocarriers include micelles, dendrimers, and polymer-drug conjugates. Nanoparticles generally vary in size from 10 to 1000 nm. The drug is dissolved, entrapped, encapsulated, or attached to a NP matrix and depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Many biodegradable polymers have been used to produce polymeric nanoparticles such as poly D L-lactic-co-glycolic acid (PLGA), poly D L-lactic acid (PLA), and polyethylene glycol (PEG). NPs have been prepared mainly by two methods: (i) dispersion of the preformed polymers; and (ii) polymerization of monomers (Soppimath, Aminabhavi et al. 2001).

The nanoscopic size of NPs facilitates intracellular uptake. NPs have the ability to encapsulate therapeutic agents and release them in a controlled manner to specifically target diseased cells. NP encapsulation also improves the solubility of unmodified drug compounds. The advantages of NPs have brought widespread attention to the field of nanomedicine, including their large ratio of volume to the surface area, modifiable external shell, biodegradability, and low cytotoxicity (Davis, Chen et al. 2010). Surface modification with polyethylene glycol (PEG) protects NPs from clearance from the blood by the mononuclear phagocytic system (MPS), markedly increasing both circulation times and drug uptake by target cells. Functionalization of the NP surface with multivalent targeting moieties not only improves drug efficacy but simultaneously reduces the dose, providing a novel method to optimize drug pharmacokinetics. NPs spatially localize through passive/active targeting and are capable of delivering drugs through epi/endothelial barriers (Zhong, Meng et al. 2014, Xu, Ho et al. 2015).

2.1.3. Inorganic

Inorganic nanocarriers have been used due to their properties, such as chemical composition, size, shape, good stability, ease of functionalization, and high surface-to-volume ratio. Inorganic nanoparticles include gold nanoparticles, magnetic nanomaterials, carbon nanotubes, silica nanoparticles, and quantum dots. Gold nanoparticles have received attention due to their unique properties. These nanoparticles are easily synthesized and size can be controlled. These nanoparticle conjugates can exhibit increased targeting of rapid transport kinetics, long circulatory half-life, size-enhanced tumor uptake, and biocompatibility. These nanoparticles represent one of the most stable and easily surface functionalized for molecular conjugation. The shape of gold nanoparticles has been demonstrated to penetrate the cell membrane. Thiol stabilized gold nanoparticles were used to demonstrate enhanced CT image contrast and increased radiosensitivity of prostate tumors (Azzawi, Seifalian et al. 2016). Quantum dots (QDs) are inorganic fluorescent semiconductor nanoparticles composed of 10-50 atoms with a diameter ranging from 2 to 10 nm (Zhao, Cheng et al. 2018).

In recent years, QDs have attracted the attention of many research groups. The broad absorption and narrow emission characteristics of the QDs make it possible to perform multicolor imaging with a single excitation source. The high fluorescence quantum yield of the QDs, their resistance to photobleaching and their unique physical, chemical and optical properties make them good candidates for fluorescent tagging for in vivo molecular, cellular imaging especially for intraoperative tumors (Tsai, Chen et al. 2009, Misra, Acharya et al. 2010).

2.2. Nanocarriers and Multidrug Resistance

Multidrug resistance (MDR) is one of the major challenges in cancer treatment, which occurs in a short period during/after clinical treatment, and may result in cross-resistance to many other structurally and mechanically different chemotherapeutics. It can be classified into two types: acquired MDR that can be developed during traditional chemotherapy in common doses and intrinsic MDR that can be developed from preexisting resistance present in tumor cells. If there is tumor recurrence, chemotherapy may fail because of residual drug-resistant cells dominating the tumor population. Chemotherapy will kill only drug-sensitive cells, leaving behind drug-resistant cells that overexpress MDR transporters. The main drug efflux transporters include P-glycoprotein, multidrug resistance-associated proteins (MRP1 or ABCC1), and the breast cancer resistance protein (ABCG2). To circumvent MDR, an optimal drug delivery system has to release drugs into the cytoplasm rapidly and completely, leading to sufficiently high intracellular drug concentration to exceed drug efflux and limit concentration, in order to inhibit the proliferation of drug-resistant cancer cells and kill them. Recently, nanotechnology has been reported to overcome MDR, including nanocarriers. A study found a non-ionic copolymer with a hydrophobic core containing doxorubicin, called SP1049C, has been shown to circumvent p-glycoprotein-mediated drug resistance.

2.3. Passive nanoparticle target

Nanoparticles circulating in the bloodstream can reach the neoplastic tissue by passive drug targeting through the enhanced permeation and retention effect (EPR). When a solid tumor reaches a certain size, the normal vasculature present in its early stage is not sufficient enough to provide the oxygen required for proliferation. Because of this, the cells start to die and they secrete growth factors, which trigger angiogenesis, where the budding of new blood vessels from the surrounding capillaries occurs, increasing their permeability. Angiogenesis in tumors is the process of the rapid development of new, irregular blood vessels that present a discontinuous epithelium and lack the basal membrane of normal vascular structures. Fenestrations in the capillaries, depending on the location and tumor type, can reach sizes from 200 to 2000 nm. The fenestrations between endothelial cells facilitate the extravasation of nanocarriers from the surrounding vessels into the tumor. Free drugs may diffuse nonspecifically and a nanocarrier can extravasate into the leaky vessels of tumor tissues through the EPR effect. A study using liposomes of different sizes suggests that particles with a diameter of 200–300 nm are able to extravasate, whereas in another part of the same tumor, molecules that are only a few nanometers in size may have difficulty entering the interstitium.

2.4. Active nanoparticle target

Passive targeting is available only in certain types of tumors and does not, necessarily, ensure the internalization of nanocarriers by targeted cells. Nanocarriers can be engineered to attach targeting with selective agents to employ active targeting. The objective of passive targeting is to increase interactions between nanoparticles and cells and to enhance the internalization of drugs without altering biodistribution. Some physicochemical properties might also affect the efficacy of active targetings, such as the size of nanoparticles, choice of the targeting ligand, and ligand density. The nonspecific binding of proteins during the nanoparticles dislocation through the bloodstream and the administration route has been shown to affect the targeting ability of nanocarriers. Active targeting can be used for controlled drug release applications, where the drug is released into the extracellular or intracellular environment.

3. BREAST CANCER

3.1. Incidence and epidemiology

Breast cancer is the most common cancer for females both in the USA and other countries in the world. Breast cancer is the leading cause of cancer death among women aged 20–59 years old and the second leading cause of cancer death among women aged 60 years or older behind lung and bronchus cancers. The overall 5 years relative survival rate of women with breast cancer in the USA increased due to improved techniques for diagnosis and treatment. However, the 5 years relative survival rate of breast cancer patients diagnosed at late stages is still low and a common cause of breast cancer mortality is metastasis to lymph nodes, lung, liver, bone, and brain (Tang, Loc et al. 2017).

3.2. Types of Breast Cancers

The origin of breast cancer is associated with breast tissues especially from the inner lining of the milk ducts and lobules. The common breast tumor types include, 1) either oestrogen receptor or progesterone receptor-positive where HER2 is negative, 2) either progesterone receptor-positive or oestrogen receptor-positive where HER2 is positive, 3) oestrogen receptor and progesterone receptor negative where HER2 is positive (HER2 positive) and 4) all oestrogen, progesterone and HER2 are negative (triple-negative) (Weerathunga and De Silva 2017).

3.3. Current Breast Cancer Diagnosis

Breast cancer diagnosis, according to the European guidelines, is based on clinical examination in combination with imaging and confirmed by pathological assessment. Clinical examination includes manual palpation of the breasts and locoregional lymph nodes, along with assessment for distant metastases. Other forms of assessment include complete personal and family medical history, including evaluation of menopausal status, physical examination, blood count analysis, liver and renal function tests, and alkaline phosphatase and calcium checks.

Pathological diagnosis should be based on core-needle biopsies obtained by manual or preferably by ultrasound or stereotactic guidance. The pathological report should include the histological type,

grade, estrogen receptor (ER), and for invasive cancer, progesterone receptor (PgR) along with human growth factor receptor type 2 (HER2). Routine staging evaluations are directed at locoregional diseases, as asymptomatic distant metastases are very rare and patients do not earn profit from comprehensive laboratory and radiological staging. Bilateral mammography and ultrasound of the breast and regional lymph nodes are included in imaging (Rocha, Chaves et al. 2017).

3.4. Breast cancer treatment

Breast cancer treatments are surgery, radiation, chemotherapy, hormone therapy, targeted therapy and immunotherapy. Most women with breast cancer have some type of surgery as part of their treatment. For nonmetastatic breast cancer, the main goals of therapy are eradicating tumors from the breast and regional lymph nodes and preventing metastatic recurrence. Local therapy for nonmetastatic breast cancer consists of surgical resection and sampling or removal of axillary lymph nodes, with consideration of postoperative radiation. Systemic therapy may be preoperative (neoadjuvant), postoperative (adjuvant), or both (Waks and Winer 2019). However, a significant shortcoming associated with these therapies is the lack of specificity, which leads to reduced therapeutic efficiency and serious side effects. Even though it is not common, doxorubicin, paclitaxel, and some other chemo drugs can cause permanent heart damage when the drugs are used in high doses or for a long time or in combination with trastuzumab. Taxanes (docetaxel, paclitaxel, and protein-bound paclitaxel), platinum agents (carboplatin, cisplatin), vinorelbine, eribulin, and ixabepilone, can damage nerves in the hands and arms and feet and legs (Partridge, Burstein et al. 2001, Shapiro and Recht 2001). Besides, the poor distribution and penetration of drugs in solid tumors result in incomplete tumor response and multiple drug resistance. After primary treatments with surgery, drugs are used as adjuvant therapy that treats residual micro-metastases. However, most cancers that recur are ultimately fatal because systemic therapies do not eradicate gross metastatic disease (Minchinton and Tannock 2006).

4. NANOMEDICINE FOR BREAST CANCER TREATMENT

Systemic antitumor pharmaceuticals are usually hydrophobic, untargeted, and toxic compounds, which can cause severe side effects. Nanomedicine with its advantages shows great potential in breast cancer treatment. Many nanoparticulate-based chemotherapeutic delivery platforms of doxorubicin and paclitaxel have been approved by the FDA and in several countries: Doxil®, Myocet®, Lipodox®, Lipusu®, Abraxane®, Genexol-PM®, Nanoxel®. Moreover, the other nano- based formulations that are circulating in the market are DaunoXome® (liposomal daunorubicin) and Kadcyla® (Ado-trastuzumab emtansine). In this article, we also present nanotherapies that are in clinical trials in breast cancer patients.

4.1. Anthracycline

Anthracycline-based (doxorubicin, daunorubicin, epirubicin) regimens have been important components especially for patients with breast cancer. As demonstrated, anthracycline-based regimens decrease breast cancer mortality by 20–30%. Anthracycline toxicities include the rare—but potential morbid—cardiotoxicity or leukemogenic effect, and the almost universal—but very distressing—alopecia. Due to potential toxicities, and a large number of patients being exposed, several worldwide trials have re-examined the

role of anthracycline-based regimens in the management of breast cancer. Current literature supports that anthracyclines are not required for all patients with breast cancer and should be avoided in those with high cardiac risk. Patients with intermediate or high-risk breast cancer should be considered for anthracycline-based regimens based on other factors such as age, comorbidities, tumor grade, lymphovascular invasion, and genomic profiling (Jasra and Anampa 2018). To overcome, nano-delivery systems have emerged. Nanotechnology offers potential solutions to the historical challenge that has rendered breast cancer so difficult to contain and eradicate: the extreme biological diversity of the disease presentation in the patient population and in the evolutionary changes of any individual disease, the multiple pathways that drive disease progression, the onset of 'resistance' to established therapeutic cocktails, and the gravity of the side effects to treatment, which result from generally very poor distribution of the injected therapeutic agents in the body (Tanaka, Decuzzi et al. 2009). Up until now, many anthracycline nano-delivery systems have been developed and reported both in vitro and in vivo, and some of these systems have even advanced to clinical trials (Ma and Mumper 2013).

4.1.1. Doxorubicin

Doxil®, PEGylated liposomes encapsulating doxorubicin was the first FDA-approved nanomedicine in 1995. The compounds, which contribute to the reduced systemic toxicity and increased circulation time. To achieve longer *in vivo* circulation of liposomes, biocompatible and inert polymers such as PEG are coated on the surface of liposomes, forming a protective layer, which decreases the recognition by the subsequent clearance. Anhorn *et al*. have developed doxorubicin-doped human serum albumin nanoparticles (DOX-NP) surface-functionalized with trastuzumab via covalent binding (DOX–NP–trastuzumab). DOX–NP–trastuzumab bound to 73% of HER2 overexpressing SK-Br-3 breast cancer cells, while the DOX–NP bound to less than 6% of SK-Br-3 cells (Tang, Loc et al. 2017). Hyaluronic acid-modified carbon dot-doxorubicin nanoparticles drug delivery platform, which provides a strategy for targeted therapy. CD44 targeted HA-modified carbon dots (HA-CDs) were synthesized as carriers by one-step hydrothermal treatment within one. The as-prepared HA-CDs were then loaded with doxorubicin (HA-CD-CBA-DOX) via an acid-cleavable bond. In in vitro experiments, the formulation displayed good hemocompatibility and serum stability, while exhibiting high cytotoxicity on 4T1 cells. Compared with free DOX, superior in vivo anti-tumor efficacy was observed in both heterotopic and orthotopic 4T1 cell tumor models (Li, Li et al. 2020). Pluronic P123 modified nano micelles loaded with doxorubicin enhanced tumor-suppressing effect on drug-resistant breast cancer cells. The expression of P-gp (the key mechanism of multi-drug resistance (MDR) in cancers and MDR1 (P-gp encoded by MDR1) gene was highly expressed in MCF-7R but not MCF-7 cells. The cellular uptake of Dox-loaded NMs: P123-PEG2000-DSPE (Dox) was higher than that of free Dox and not loaded NMs: PEG2000-DSPE (Dox) in MCF-7R cells In addition, the P123-modified NMs inhibited the expression of P-gp and MDR1 (Zhang, Chen et al. 2020). PEGylated chitosan/doxorubicin nanoparticles and conjugated with monoclonal antibodies can be used for breast cancer therapy. Chitosan nanoparticles (CSNP) have been selective and sustained release of doxorubicin (DOX) within tumor microenvironment. Chitosan nanoparticles (CSNP) with Polyethylene glycol (PEG) was performed to enhance its blood circulation time without being opsonized or captured by the immunogenic reticuloendothelial system (RES). There are two different types of cancer-specific monoclonal antibodies (mAb) and this functionalization has the potential of evading systemic side effects of parenteral free DOX (Zidan 2020). Quercetin, the plant-derived phenolic compound, plays a pivotal role in controlling hemostasis, by having potent antioxidant and free-radical

scavenging properties. This flavonoid in combination with chemotherapeutic drugs improves the efficacy of these agents in the induction of apoptosis in cancer cells. Nano-quercetin (phytosome) in doxorubicin-induced apoptosis, which was investigated (Minaei, Sabzichi et al. 2016). In addition, breast cancer in women are regarded as major health burdens, accounting for the majority of cancer diagnoses globally. Doxorubicin (DOX) resistance in the breast represents the main reason for unsuccessful therapy. And the researchers explore selenium nanoparticles (nano-Se) to overcome this resistance obstacle of DOX nanoparticles (nano-DOX) in these cancerous cells (Abd-Rabou, Ahmed et al. 2020).

4.1.2. Epirubicin

One of the potent anthracyclines, epirubicin (EPI), has been encapsulated in PLGA nanoparticles (NPs) conjugated by trastuzumab, as a monoclonal antibody (mAb). In vitro cellular experiments on overexpressing human epidermal growth factor receptor 2 (HER2) positive and negative cell lines demonstrated that mAb conjugated EPI-NPs has more cytotoxicity and drug uptake on overexpressed HER2 receptor cells in comparison to HER2 negative ones (Derakhshandeh, Khaleseh et al. 2019). A glassy carbon electrode (GCE) was modified with cerium-doped ZnOnanoflowers (Ce-ZnO/GCE) to obtain a sensor for direct simultaneous detection of the cancer drugs epirubicin and methotrexate. Diffusion coefficients and heterogeneous rate constants were determined for the oxidation of epirubicin. The method was applied to the simultaneous determination of epirubicin and methotrexate in pharmaceutical injections and in spiked diluted blood specimens (Jandaghi, Jahani et al. 2020). Non-toxic and biocompatible carriers are provided by human serum albumin nano-capsule (HSA/NC) for drug delivery applications and HSA, with high loadings of drug-modified cobalt ferrite (CoFe2O4) magnetic nanoparticle (CoFe2O4/MNPs) was fabricated for epirubicin anticancer drug delivery. IC50 for free epirubicin, unloaded CoFe2O4/MNPs/HSA/NC, CoFe2O4/MNPs and epirubicin-loaded CoFe2O4/MNPs/HSA/NC were 7.7, 2400, 840 and 430 μg/ml, respectively. The results revealed high cytotoxicity effect of epirubicin-loaded CoFe2O4/MNPs on breast cancer cell lines (Karimi, Shojaei et al. 2017).

4.1.3. Daunorubicin

DaunoXome or liposomal Daunorubicin was approved in several countries, including the USA for the treatment of Kaposi's sarcoma (KS) in HIV-positive patients. The formulation was reviewed as particularly effective for solid tumor targeting consists daunorubicin in SUVs composed of highly pure distearoylphosphatidyl choline and cholesterol in a 2:1 mole ratio, encapsulating the citrate salt of daunorubicin within the inner aqueous core at a lipid:drug weight ratio of 18.7:1. Preclinical investigations have indicated that DaunoXome® increases in vivo daunorubicin tumor delivery by about 10-fold over a conventional drug, yielding a comparable increase in therapeutic efficacy. Investigations on the modes of delivery and of action indicate that DaunoXome® arrives at and accumulates within tumor cells primarily in an intact form. Once within the tumor cells, the liposomes release the drug over a prolonged period (36 h or more), providing sustained, high levels of cytotoxic material within tumor cells (Forssen 1997).

A study in 16 women with metastatic breast cancer showed that the maximum tolerated dose was 120 mg/m2, and the related toxicity observed was mild and manageable (asymptomatic cardiotoxicity, neutropenia or neutropenic pyrexia). Tumor's response was evaluable in 15 patients, of whom two had objective responses, six had stable disease and seven had progressive disease (O'Byrne, Thomas et al. 2002).

4.2. Taxanes

Taxanes, and in particular the currently available paclitaxel (Taxol®; Bristol-Myers Squibb Co, Princeton, NJ, USA) and docetaxel (Taxotere®; Aventis Pharmaceuticals Inc, Bridgewater, NJ, USA), represent an important class of antitumor agents which have proved to be fundamental in the treatment of advanced and early-stage breast cancer. Both these drugs are included in the treatment regimens for adjuvant chemotherapy and are indicated as preferred agents for recurrent and metastatic breast cancer by The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for breast cancer (Network 2008).

However, their chemical formulations are highly hydrophobic molecules and Cremophor EL and Tween 80 are used as lipid-based solvents. This induces serious and dose-limiting toxicities (e.g. hypersensitivity reactions, hyperlipidemia, abnormal lipoprotein patterns, aggregation of erythrocytes, neutropenia) (Gelderblom, Verweij et al. 2001, McClay 2011). Therefore, nano-formulations, particularly for paclitaxel are developed to improve the solubility without Cremophor EL and increase the circulation time of the drug.

4.2.1. Paclitaxel

Abraxane® (Albumin-bound paclitaxel ABI-007) was approved by FDA in 2005 for pretreated metastatic breast cancer patients. ABI-007 is a novel, albumin-bound, 130-nm particle formulation of paclitaxel, free from any kind of solvent. It is used as a colloidal suspension derived from the lyophilized formulation of paclitaxel and human serum albumin diluted in saline solution (0.9% NaCl). In detail, human serum albumin stabilizes the drug particle at an average size of 130 nm which prevents any risk of capillary obstruction and does not necessitate any particular infusion systems or steroid/antihistamine premedication before the infusion (Miele, Spinelli et al. 2009). In the phase III trial, ABI-007 demonstrated greater efficacy and a favorable safety profile compared with standard paclitaxel in this patient population. The response rates were significantly higher (14%) and the time to tumor progression was significantly longer when compared with standard Paclitaxel. The incidence of grade 4 neutropenia was significantly lower for ABI-007 compared with standard paclitaxel (9% *v* 22%, respectively; $p < .001$) despite a 49% higher paclitaxel dose (Gradishar, Tjulandin et al. 2005, Lee, Park et al. 2020). Lipusu was officially used in China in 2006 for non-small-cell lung cancer and breast cancer treatment. This liposomal formulation was shown to retain the antitumor activity of the free drug while the toxicity was reduced compared to Taxol(R) both in vitro and in vivo (Yang, Li et al. 2006).

Genexol® and Nanoxel® are polymeric micelles-based formulations of paclitaxel which are used in several countries for treating breast cancer. The polymeric micelle formulation of Genexol® is composed of hundreds of low molecular weight, nontoxic, and biodegradable amphiphilic diblock copolymers which include monomethoxy poly (ethylene glycol)-blockpoly (D,L-lactide), and has a great potential in terms of water solubility, in vivo stability, and the nanoscopic size (a diameter of 20–50 nm) of the micellar structure. Phase II study confirmed the significant activity of Genexol-PM at 300 mg/m2 given every 3 weeks in first-line or anthracycline-pretreated patients with MBC. The overall response rate was 58.5%, which can be compared favorably to the response rate of 47.6% produced by ABI-007. The main AEs of Genexol-PM were neutropenia and sensory PN. In this study, the combined incidence of grade 3 and 4 neutropenia was 68.3%, while this incidence in a phase II trial of ABI-007 was 50.8%. However, the incidence of grade 4 neutropenia was 17.1% in this trial, which is lower than that of 23.8% shown in the ABI-007 trial. No patients were complicated by neutropenic fever in this study (Kim, Kim et al. 2004,

Lee, Chung et al. 2008). In phase III trial, Genexol-PM allows administration of an increased dose of paclitaxel, offering significantly improved efficacy without compromising patient safety (Park, Sohn et al. 2017). Nanoxel® contains a co-polymer of N-isopropyl acrylamide (NIPAM) and vinylpyrrolidone (VP). This polymer is biodegradable and amphiphilic and it forms nanometer-sized micelles (mean particle size 80 nm) when exposed to water. Paclitaxel is released slowly by surface erosion of the hydrophilic polymer. The nanoparticle size of 80 nm permits selectively into the tumor cells, utilizing the enhanced vascular permeability associated with tumorigenesis while sparing normal tissue. Nanoxel is shown to have minimized toxicity, along with an increase in the antitumor activity, due to selective accumulation of the drug in tumors (Madaan, Singh et al. 2013). At a dose of 300 mg/m^2 Nanoxel demonstrated a better overall response and clinical benefit compared with CrEL paclitaxel 175 mg/m^2. Nanoxel at a dose of 220 mg/m^2 showed a better efficacy and safety profile than conventional paclitaxel (175 mg/m^2). The incidence of musculoskeletal events, gastrointestinal toxicity, and skin/subcutaneous toxicity were comparable in all the treatment arms. According to Indian experts, the nanoparticle polymer-based paclitaxel formulation was well-tolerated and could be safely administered without any premedication (Rajappa, Joshi et al. 2018).

There are some other remarkable CrEL- free formulations of paclitaxel that are undergoing clinical trials, such as EndoTAG-1, LEP-ETU and NK105. LEP-ETU is a well-characterized novel lyophilized liposome-based paclitaxel formulation that is sterile, stable and easy to use. The mean particle size of the liposomes is about 150 nm before and after lyophilization, and the drug entrapment efficiency is greater than 90%. Stability data indicated that the lyophilized LEP-ETU was physically and chemically stable for at least 12 months at 2–8 and 25°C (Zhang, Anyarambhatla et al. 2005). LEP-ETU showed bioequivalence with paclitaxel formulated with polyethoxylated castor oil (Slingerland, Guchelaar et al. 2013), safety and good tolerance in advanced cancer (including breast cancer) (Fetterly, Grasela et al. 2008). These results suggest that LEP-ETU could be an alternative to conventional PTX.

EndoTAG-1 is a cationic liposomal formulation composed of 1,2-Dioleoyl-3-Trimethylammonium Propane (DOTAP), dioleolylphosphatidyl choline and paclitaxel at a molar ratio of 50:45:5, showing a particle size of 180–200 nm and a positive zeta potential. Thus, ET targets activated solid tumor endothelial cells that express negatively charged cell-surface molecules (Fasol, Frost et al. 2012). Awada et al, in a randomized controlled phase II trial in 140 patients with triple-negative breast cancer, concluded that a combination of EndoTAG-1 and standard paclitaxel therapy showed good tolerance and antitumor efficacy (Awada, Bondarenko et al. 2014). In another study in 20 patients with HER2-negative breast cancer, the mean % reduction in MRI estimated tumor volume at the end of EndoTAG-1 plus paclitaxel treatment was 81% (Ignatiadis, Zardavas et al. 2016). NK105 is a polymeric micelles-based, passive targeting formulation of paclitaxel that is undergoing a phase III clinical trial. PEG constituted the outer shell of the micelle, which conferred a stealth property on the drug that allowed the micellar drug preparations to be less avidly taken up by the reticuloendothelial system (RES) and to be retained in the circulation for a longer time (Hamaguchi, Matsumura et al. 2005). It has been reported to exert antitumor activity *in vivo* and to have reduced neurotoxicity and more potent radiosensitizing agent as compared to that of free PTX (Hamaguchi, Matsumura et al. 2005, Hamaguchi, Kato et al. 2007). An open-label phase III non-inferiority trial to compare the efficacy and safety of NK105 and PTX in metastatic or recurrent breast cancer was conducted by Yasuhiro F et al in 2019. The results in 436 patients indicated that there was no difference in progression-free survival but NK105 had less toxicity in the nervous system than standard paclitaxel. The incidence of peripheral sensory neuropathy (PSN) was 1.4% vs. 7.5% (≥Grade 3) for NK105 and PTX, respectively (Fujiwara, Mukai et al. 2019).

4.2.2. Docetaxel

Docetaxel, another member of the taxane family can be encapsulated within calcium phosphosilicate nanoparticles (CPSNPs), which can be surface functionalized with either PEG and retention effects or anti-CD71 for active targeting to breast cancer cells. CD71-Docetaxel–CPSNPs can provide prolonged circulation time, enhanced accumulation and targeting, and improved drug efficiency with reduced or eliminated side effects (Tang, Loc et al. 2017). Docetaxel (DTX) also encapsulated lipid polymer hybrid nanoparticles (LPHNPs-DTX) were prepared by self-assembled nano-precipitation technique. In-vitro cell studies showed better cytotoxicity and greater cellular uptake of docetaxel at lower IC50 and improved apoptosis. In-vivo studies exhibited better pharmacokinetics and tumor targetability with the least drug distribution in various organs with LPHNPs-DTX as compared with free DTX. A noticeable % reduction in tumor burden was observed with LPHNPs-DTX as compared with free DTX (Jadon and Sharma 2019). Metal-organic frameworks, such as MIL-100, have been recently introduced as promising drug carriers due to their notable characteristics such as stability, biocompatibility and owning large porosity which may admit a broad range of drugs with different molecular sizes. This is the first time that docetaxel (DTX) as a highly hydrophobic anticancer drug was encapsulated in nanoMIL-100 with a drug payload of 57.2 wt%. The *in vitro* release of DTX from the prepared nanocarrier was investigated in two pH values, 7.4 and 5.5. The toxic effect of DTX-loaded nanoMIL-100 was examined on human breast cancer cell line, MCF-7, and a significant decrease was observed in IC_{50} value (0.198 μg/mL) at the first 24 h in comparison with the free drug (4.9908 μg/mL) (Rezaei, Abbasi et al. 2018). Docetaxel (DTX) and gemcitabine (GEM) with linker poly-ethylene-glycol (PEG) to develop amphiphilic molecules having self-assembled properties. The synthesized conjugate (DTX-PEG-GEM) demonstrated critical micelle concentration (CMC) in the range of 5–10 μg/ml which self-assembled to form NPs with size 124.2 ± 5.7. Tumor growth inhibition study demonstrated a significant reduction in tumor volume and a higher survival rate with NPs. Moreover, NPs demonstrated significantly lower hepato- and nephrotoxicity (Kushwah, Katiyar et al. 2018).

4.3. Cisplatin

Platinum anticancer drugs, such as cisplatin, the most potent member of the platinum drug family, penetrate the nucleus of cancer cells and form adducts with DNA leading to apoptosis (Florea and Büsselberg 2011). The most significant, dose-limiting toxicities of Cisplatin therapy are neurotoxicity and nephrotoxicity, both of which are strongly influenced by peak plasma concentration (Hartmann, Kollmannsberger et al. 1999). Lipoplatin, which was approved in 2015 for metastatic pancreatic adenocarcinoma, is a liposomal nanoparticle of 110 nm diameter that carries cisplatin. With the promising early data, Lipoplatin has been extensively evaluated and has successfully completed a number of clinical studies from Phase I to III trials. Its official indication is for non-small cell lung cancer. In a number of clinical trials, Lipoplatin demonstrated enhanced cisplatin retention in tumor tissue and substantially reduced renal toxicity, peripheral neuropathy, ototoxicity and myelotoxicity. This product also has the potential to be included in the treatment of breast cancer. In a Phase II study of Lipoplatin/vinorelbine combination in HER2/neu-negative metastatic breast cancer, complete response and partial response were achieved in the majority of patients (9.4% and 43.8%, respectively), with only 9.4% showing disease progression. No grade 3/4 nephrotoxicity or neuropathy, both key toxicities of cisplatin, was noted (Boulikas 2009, Farhat, Temraz et al. 2011). Paclitaxel and cisplatin co-loaded in poly(2-oxazoline) polymeric micelle

formulations display a broad range of drug mixing ratios and exceptionally high two-drug loading as well as the slowed-down release of the drugs to the serum as a result of their co-loading. Simulations of PK for the micelle, serum and tumor compartments in a three compartmental model suggest that the decreased rates of drug release from the micelles to the serum can result in improved tumor drug delivery provided that the micelles display high enough ability to penetrate in the tumor. The improved PK and increased tumor distribution for both drugs as a result of their formulation in one micelle is demonstrated for the animal tumor model. The superior performance of these formulations *in vivo* is further reinforced by an increased anti-tumor efficacy in breast and ovarian cancer models (Wan, Beaudoin et al. 2019).

4.4. Trastuzumab Emtansine

Trastuzumab is one of the anti-HER2 targeted therapies, which was used in HER2-positive breast cancer patients. Trastuzumab emtansine, consisting of trastuzumab coupled to a cytotoxic agent, emtansine (DM1), by a stable linker, has been approved in 2013 by the European Medicine Agency, in 2018 in Canada, and in 2019 by FDA. Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that incorporates the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine); the antibody and the cytotoxic agent are conjugated using a stable linker. Due to the high stability of the linker, DM1 is released only after proteolytic degradation of the antibody part (Erickson, Park et al. 2006). Thus, this therapy allows intracellular drug delivery specifically to HER2-overexpressing cells, increases the antitumor effect and potentially limits damage to healthy tissues, and improves the survival of HER2-positive breast cancer patients with metastatic and locally recurrent unresectable disease or relapse within 6 months of the end of adjuvant therapy [63]. In phase III clinical trial with 991 patients randomly divided into two groups, median progression-free survival was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine and median overall survival at the second interim analysis crossed the stopping boundary for efficacy (30.9 months vs. 25.1 months). The objective response rate was higher with T-DM1 (43.6%, vs. 30.8% with lapatinib plus capecitabine; $p<0.001$) (Guerin, Sabatier et al. 2015). Furthermore, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone [64]. A lower incidence of grade 3 or worse adverse events such as neutropenia, diarrhea and febrile neutropenia was reported with trastuzumab emtansine than with other drugs (physician's choice) [65].

4.5. Tamoxifen

Tamoxifen (TAM) is a hydrophobic anticancer agent and a selective estrogen modulator (SERM), which acts by promoting cancer cell death by down-regulating the action of ERs. TAM was approved by the FDA for hormone therapy of breast cancer (BC). Despite having striking efficacy in BC therapy, concerns regarding the dose-dependent carcinogenicity of TAM persist, restricting its therapeutic applications. Therefore, many attempts to fabricate TAM-loaded-nanoformulations from various nanomaterials have been made: liposomes, micelles, and other types of nanoparticles (polymeric nanoparticles (PNPs); solid lipid nanoparticles (SLNs); liquid crystalline nanoparticles-LCNPs; metallic nanoparticles (MNs); Protein-based nanoparticles). Additionally, TAM can also be employed as a *guiding vector*, directing the delivery of nanosystems containing other therapeutic agents to cancer cells. Despite recent advances of novel TAM nanoformulations, they have not completed the regulatory assessments required to proceed with clinical development (Day, Hickey et al. 2020). Based on biodegradable/biocompatible polymers,

tamoxifen-encapsulated nanocapsules were synthesized to target the folate receptor-positive breast cancer cells. The free tamoxifen has low solubility in physiological solutions, the synthesized tamoxifen-encapsulated nanocapsules have enough solubility, good stability, and more biocompatibility in these solutions. The cytotoxicity test exhibit that the mean IC50 values on the MCF-7 cell line were found to be 15.52 and 8.46 μg/ml in 24 h and 48 h respectively and the cytotoxicity increased by approximately 2.72-fold compared with free TAM against the MCF-7 cancer cell line (Nankali, Shaabanzadeh et al. 2020). The effects of lipid composition on the physicochemical and technological properties of a multidrug carrier (MDC) containing both gemcitabine (GEM) and tamoxifen (TMX), as well as its *in vitro* antitumor activity on different breast cancer cell lines, were investigated. In particular, the following three different liposomal formulations were prepared: formulation and only formulation A: DPPC/Chol/DSPE-mPEG2000 (6:3:1 molar ratio) showed the best encapsulation efficiency between the two compounds. An MDC of formulation A was used to effectuate the *in vitro* cytotoxicity experiments (MTT-test) on MCF-7 (Cosco, Paolino et al. 2012).

4.6. Cyclophosphamide

Cyclophosphamide (CP) is one of the widely used anticancer agents; however, it has serious deleterious effects on normal host cells due to its nonspecific action. The essential trace element Selenium (Se) is suggested to have chemopreventive and chemotherapeutic efficacy (Bhattacharjee, Basu et al. 2017).

In a study 2012, gliadin and gliadin-gelatin composite nanoparticles were synthesized by the electrospray deposition system for delivery and controlled release of cyclophosphamide. Cyclophosphamide was gradually released from the gliadin nanoparticles for 48h. In contrast, the gliadin-gelatin composite nanoparticles rapidly released cyclophosphamide. Furthermore, they demonstrated that breast cancer cells cultured with cyclophosphamide-loaded 7% gliadin nanoparticles for 24h became apoptotic (Gulfam, Kim et al. 2012).

4.7. Vinorelbine

Vinorelbine (VLB) is a semi-synthetic Vinca alkaloid that is currently used in the treatment of different cancer types mainly advanced breast cancer (ABC). However, its marketed formulation has been reported to have serious side effects, such as granulocytopenia, which is the major dose-limiting toxicity. Other unwanted effects include venous discoloration and phlebitis proximal to the site of injection, as well as localized rashes and urticaria, blistering, and skin sloughing.

First, a study was to prepare, characterize, and determine the in vitro efficacy of vinorelbine-loaded sterically stabilized, biocompatible, and biodegradable phospholipid nanomicelles (SSM; size, ∼15 nm). Our results indicated that vinorelbine was incorporated at high quantities and within the interface between the core and palisade sections of the micelles. The nanomicellar formulation of vinorelbine was ∼6.7-fold more potent than vinorelbine dissolved in DMSO on the MCF-7 cell line. Therefore, these data indicate that vinorelbine-loaded SSM can be developed as a new, safe, stable, and effective nanomedicine for the treatment of breast and lung cancers (Bahadori, Topçu et al. 2014). For the invasive breast cancer cells, regular chemotherapy cannot eradicate and the residual cancer cells will form vasculogenic mimicry (VM) channels under hypoxic conditions to provide nutrients for cancer masses prior to angiogenesis. This phenomenon is a major reason for the recurrence of invasive breast cancer after treatment. In 2015, a novel type of targeted liposomes was developed by modifying a mitochondria-tropic material,

D-a-tocopheryl polyethylene glycol 1000 succinate- triphenylphosphine conjugate (TPGS1000-TPP), to encapsulate sunitinib and vinorelbine separately and a combination of the two targeted drug liposomes was used to treat invasive breast cancer. The results determined that the functional material (TPGS1000-TPP) and suitable size of the liposomes (90–100 nm) resulted in prolonged blood circulation, enhanced permeability retention (EPR) effect in cancer tissue, and a mitochondrial targeting effect. Targeted drug liposomes were internalized via cellular uptake and accumulated in the mitochondria of invasive breast cancer cells or VM channel-forming cancer cells to induce acute cytotoxic injury and apoptosis (Shi, Sun et al. 2015).

4.8. 5-Fluorouracil

Magnetic 5-FU-IP is promising for breast cancer therapy with high efficacy. In 2016, magnetic molecularly imprinted polymer (MIP) was synthesized by using polydopamine for controlled 5-fluorouracil (5-FU) delivery in a spontaneous model of breast adenocarcinoma mice in the presence of an external magnetic field. Results showed higher efficacy of 5-FU-IP in the presence of a magnetic field upon suppressing tumor growth than free 5-FU and 5-FU-IP without magnetic field. The 5-FU and Fe distribution among tissues were evaluated by high-performance liquid chromatography and flame atomic absorption spectrometry, respectively. The obtained results showed a significant deposition of 5-FU in the 5-FU-IP treated group with a magnetic field (Hashemi-Moghaddam, Kazemi-Bagsangani et al. 2016). In 2019, they have also synthesized a prodrug of 5-fluorouracil (5FU) covalently conjugated to low molecular weight chitosan (LMWC) via a photocleavable linker. The conjugate showed enhanced water solubility compared to LMWC and formed hydrogel and DMSO gel. The conjugate polymer was also fabricated into nanoparticles by ionic gelation technique. The size of the nanoparticles was found to be in the range 70–90 nm, thus should have the ability to penetrate into living cells. In vitro release study of 5FU from the conjugate showed a controlled release of the antitumor drug over time (Horo, Das et al. 2019). In addition, drug resistance is a major challenge of breast therapy leading to treatment failure. Nano-Se (selenium) and nano-FU were synthesized and characterized, then applied individually or in combination upon MCF7, MDA-MB-231 cancerous cell lines. Nano-FU induced cell death in MCF7 more effectively than MDA-MB-231. Moreover, nano-FU plus nano-Se potentiate MCF7 chemo-sensitivity was higher than MDA-MB-231. It is relevant to note that Se and FU nano-formulations inhibit cancer cell bioenergetics via glucose uptake slight blockage. This novel approach could be of great potential to enhance the chemo-sensitivity in breast (Abd-Rabou, Shalby et al. 2019). Nano-curcumin decreased cell proliferation by 83.6%, which was more than that achieved by cyclophosphamide (63.31%), and 5-fluorouracil (75.04%) (Hosseini, Chamani et al. 2019).

4.9. Metformin

Metformin is used for the management of breast carcinoma basically along with other chemotherapeutics but recently the monotherapy of the drug is also in research basically for Triple Negative Breast Cancer (TNBC) (Currie, Poole et al. 2012). Even a few positive feedbacks were obtained from the ER+ and ER- breast cancer cell lines cell cycle arrest of monotherapy (Yang 2015). The combination Metformin-Curcumin proved the synergistic effects in breast cancer and killed the cancer cells more rapidly than treatment alone (Falah, Talib et al. 2017). Real-time PCR results were found that nano-encapsulated Metformin-Curcumin in PLGA/PEG (NP Met-Cur) to free combination could further decline hTERT

(in breast cancer) expression in all concentrations ($p < .05$). Met–Cur NPs were produced by the improved double emulsion W/O/W (water/oil/water) method, after synthesizing of PLGA/PEG (ring open polymerization of glycolide and DL-lactide followed by addition of PEG_{4000}). The drugs (Met and Cur) were released in a sustained manner from the nanoparticulate systems up to 120 h study period. By 120 h, $92 \pm 3.43\%$ of Met released from the NPs, whereas only $65 \pm 4.2\%$ of Cur released during the same time period. In theory speaking, Met was released at first when the outermost copolymer layer broke off, after that, the core structure with hydrophobic surface disassembled quickly, accompanied by the release of Cur. A sustained release profile for both drugs would be beneficial for efficient cancer therapy. Furthermore, a sequential release of drugs would activate the cell apoptosis in cancer tissues (Farajzadeh, Pilehvar-Soltanahmadi et al. 2018).

5. CHALLENGES AND CURRENT LIMITATIONS IN NANOMEDICINE DEVELOPMENT

Although many publications suggest that nanomedicine therapeutics are effective in breast cancer treatment, both in vitro and in vivo, there are still many difficulties before extensive clinical use of these therapies can become standard treatment protocols.

One of the major barriers is the determination of optimal physicochemical parameters, such as structure, composition, size, surface properties, porosity, charge, and aggregation behavior. Variability within these properties causes dramatic changes in secondary properties such as biocompatibility, toxicity, and in vivo outcomes. Nanocarriers may interact with other biological fluids (e.g. blood serum) or biomolecules (e.g. proteins), which may lead to aggregation or agglomeration of particles. Such interactions can significantly alter the function of nanomedicine compounds in biological systems (Bertrand and Leroux 2012, Wicki, Witzigmann et al. 2015). In addition, the discrepancy between the efficacies obtained in preclinical studies and the outcomes from clinical trials leads to the disapproval of many nanoplatforms (Choi, Lin et al. 2014).

Another obstacle in nanomedicine development is the concern of its safety. An increasing amount of data is becoming available regarding the toxicity of nanoparticles. Properties such as size, shape, surface area, surface charge, porosity, or hydrophobicity affect the behavior and performance of nanomedicine drugs at the nano-bio interface, which have been demonstrated to be associated with detrimental biological interactions. However, in clinical development, risks may be minimized by combining more advanced or even predictive diagnostic tools with novel targeting strategies (Wicki, Witzigmann et al. 2015).

Large-scale manufacturing will be more difficult when NP formulation involves multiple steps or complicated technologies. The transition from laboratory to clinic is nearly always accompanied by the optimization of formulation parameters to reduce the batch-to-batch variations of physical and chemical properties that may occur due to the polydispersity of the nanomaterial. The high costs of the raw materials contribute to the expensive nanotherapies. Therefore, the clinical benefit of nanomedicine drugs has to be large in order to offset the development and manufacturing costs and to justify higher prices compared to conventional therapeutics (Allen and Cullis 2013, Shi, Kantoff et al. 2017).

6. CONCLUSION

As a rapidly developing interdisciplinary field, cancer nanotechnology brings various perspectives beyond conventional breast cancer treatment that are potentially safer and more efficacious. To promote the treatment of breast cancer with nanotherapies, there are still many scientific contributions that can be made. For instance, emerging anticancer mechanisms have also attracted attention in reference to RNAi and PTA. RNAi focuses on the treatment of cancer at the gene level by degrading mRNA or suppressing RNA translation in cancerous cells. With nanoparticle-mediated PTA, cancer cells are eradicated by the noninvasive treatment, which is beneficial for patients that are irresponsive to chemotherapeutic or radiation treatment. Lastly, inventing novel nanocarriers is an alternate route within the scope of perspective nanotherapies. In conclusion, the versatility of nanoparticles allows for the delivery of multiple active agents with the ability to target various types of cancer. This leads to improved efficacy and advancements in both diagnosis and treatment. These unique properties make nanomedicine challenging to study, but at the same time, appealing to the scientific community aiming to improve patient outcomes.

ABBREVIATION

SUV (Small unilamellar vesicle); LUV (Large unilamellar vesicle); EPR (Enhanced permeability and retention); VEGF (Vascular endothelial growth factor); VCAM (Vascular cell adhesion molecule); NPs (Nanoparticles); HER2 (Human epidermal growth factor receptor 2); ER (Estrogen receptor); CT (Computed tomography); QDs (Quantum dots); MDR (Multidrug resistance); MRP1 (Multidrug resistance-associated protein 1); ABCC1 (ATP Binding Cassette Subfamily C Member 1); ABCG2 (ATP Binding Cassette Subfamily G Member 2); PgR (Progesterone receptor); DOX (Doxorubicin); PEG (Polyethylene Glycol); SK-Br-3 (A human breast cancer cell line); CD44 (A cell-surface glycoprotein); HA (Hyaluronic acid); CDs (Carbon dots); CBA (Acid-cleavable bond); MCF-7 (A breast cancer cell line); MCF-7R (A breast cancer cell line); NMs (Nanomaterials); DSPE (Dstearoylphosphatidylethanolamine); CSNP (Chitosan nanoparticles); RES (Reticuloendothelial system); mAb (Monoclonal antibodies); GCE (Glassy carbon electrode; EPI (Epirubicin); HSA/NC (Human serum albumin/Nano-capsule); MNPs (Magnetic nanoparticle; RNAi (RNA interference); PTA (Photothermal ablation);

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Chapter 21
Application of Bioinformatics Techniques to Screen and Characterize the Plant-Based Anti-Cancer Compounds

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ABSTRACT

Plant-based natural products provide a strong background to evaluate, predict the novel class of compounds having anti-cancer properties, as well as to explore their potential mechanism mechanisms of action. Due to the huge cost and time utilization in the traditional drug development approaches, bioinformatics plays a major role to facilitate drug discovery with less cost and time strategies. Several bioinformatics-based approaches being used recently to screen as well as to characterize the potential plant-based compounds can be used to treat several types of cancer. Some of the computational approaches are target identification, screening of compounds molecular docking, molecular dynamics simulations, QSAR analysis, pharmacophore modeling, and ADMET (absorption, distribution, metabolism, excretion, and toxicity). This chapter describes specific computational methods being used currently to screen and characterize different plant-based anti-cancer molecules by taking examples from the recent literature and discussing their advantages and limitations.

INTRODUCTION

Cancer is a major group of diseases that originates due to the uncontrolled mode of cell proliferation in the body. It can also be observed in almost all parts of the body and having the capability to spread to other parts, the phenomenon is known as *metastasis* (Ames et al., 1995; Wang et al., 2018). Cancer is considered a prominent disease in terms of global death rate, which accounts for an estimated 9.6 million deaths in 2018 as per a report given by the world health organization (WHO) (https://www.

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who.int/health-topics/cancer). Several types of cancer exist as per their origin in the part of the body, among them lung, prostate, stomach, breast, thyroid, and liver cancer are the most common types of cancer in humans (Siegel et al., 2016). The continuous increase in cancer throughout the globe exerts tremendous physical, emotional, and financial stress on individuals also creates an alarming challenge for the healthcare systems. One of the important strategies for cancer treatment is early detection followed by the use of drugs. Also, other several therapeutic approaches, such as surgery, chemotherapy, radiotherapy, and immunotherapy may be used. Other modern treatment methods such as hormonal and gene therapy were also proposed by many researchers for better cancer therapy (Henderson et al., 1991; Jin et al., 2020; Pucci et al., 2019). However, many types of side effects are associated with the conventional types of therapeutic measures such as lung fibrosis, bone necrosis, nausea, vomiting, renal damage, and so on. Therefore, the anti-cancer compounds from nature have been preferred as it is safe, low cost and less toxic. However, it is essential to understand the proper signalling pathways through which enhance proliferation occurs during *tumour* formation so that this can be used as the target for the anti-cancer compounds (Hassanpour & Dehghani, 2017; Jiang et al., 1994; Zugazagoitia et al., 2016). The higher plants are known to produce several types of compounds that can be utilized as anti-cancer compounds. Due to the large structural diversity of the plant metabolite, it is possible to search for an effective molecule for this purpose. Still, challenges exist in terms of the time, cost, and difficulty associated with identification, isolation, assessing these anti-cancer compounds in the sample (Qurishi et al., 2010; Safarzadeh et al., 2014). Mutation in specific genes is known as the major cause of human cancer. Broadly, three types of gene these genes are proto-oncogenes (enhances cell growth), tumor suppressor genes (prevents the cell division), and DNA repair genes (rectifies the error and minimizes the mutation) (Schneider & Pozzi, 2011).

In the case of normal cells, the proto-oncogenes are responsible for the production of several signalling proteins and they act in a series manner and form a cascade in the metabolism. This pathway includes membrane receptors, on which the signalling proteins bind and transcription factors in the nucleus that activate the genes for cell division. Proto-oncogenes are altered by the mutation that converts to the *oncogene,* which causes cancer. For example, MYC is a proto-oncogene that codes for the transcription factor and due to the mutations, it is converted into the oncogene, responsible for about seventy percent of cancer (Kumar & Kumar, 2013). The change that occurs from the proto-oncogene to oncogene is sometimes associated with the increase in copy numbers of the proto-oncogenes and caused by the *dominant mutation*. Mutation in the tumor suppressor genes is often associated with the incapability of inhibition of cell growth and resulting in the loss of function. This type of mutation is known as the recessive type. For example, the mutation in both copies of the genes is essential to make the cell cancerous. A common example of such a mechanism is retinoblastoma and hereditary breast cancer. Similarly, the mutation in the DNA repair genes and subsequent accumulation prevents the DNA repair mechanism, causing cancer. One common example of such type is the xeroderma pigmentosum (XP) causes skin cancer (Baeriswyl & Christofori, 2009; Lodish et al., 2000). Based on the cell of origin and types of tissue, the cancers can be broadly classified into four categories, given in Table 1

Several molecular mechanisms are involved in the metamorphosis of normal cells into cancerous cells. Also, this influences several molecules involved in the cancer progression process. As the therapeutic measures several strategies are being adopted to understand and identify the molecules, hence can be used for the suitable target for the anti-cancerous drug molecules. Some of the processes have been given in Table 2.

Table 1. Broad classification of the cancers

S.No	Name	Origin of cell/tissue types	Examples
1	Carcinoma	Epithelial cells	Lung cancer, breast cancer, prostate cancer, colon cancer, pancreas cancer
2	Sarcoma	Connective tissue, Muscle cells	Bone and cartilage cancer, cancer of the muscle
3	Myeloma	Plasma cells of bone marrow	Blood cancer, Leukaemia, and Lymphomas
4	Mixed type	Originated from two or more components of cancer,	Cancers of mesodermal, adenosquamous carcinoma, teratocarcinoma, and so on

APPLICATION OF BIOINFORMATICS IN SEARCHING PLANT-BASED ANTI-CENCER DRUG MOLECULES

Several treatment methods such as surgery, radiation therapy, chemo, biological therapy, and hormone therapy are available for cancer patients but cause a large number of side effects Thousands of drug molecules have been characterized as the anti-cancerous agent, also use of these synthetic molecules have side effects. Hence, there is a continuous search for a new, ideal and effective anticancer drug molecule by the researchers so that it kills/inactivates the cancer cells by causing minimum side effects (Boivin, 1990; Coseri, 2009; Jain et al., 2016; Yates et al., 2005). In these aspects, the chemical compounds derived from plants have been used to treat human diseases including cancer from the early years. Currently, the natural products from the plants draw increasing attention over the past few years for their potential as an effective cancer preventive as well as therapeutic properties. Several anticancer agents from plant sources have been established as anti-cancer agents such as vinca alkaloids, vinblastine, vincristine, cytotoxic podophyllotoxins, taxanes, camptothecins, and so on. Many of the other plant-based anti-cancer compounds are available in the database, represented in Table 3. Several plant-based anti-cancer agents have been characterized and they are in the pre-clinical developmental stage [47-50].

Current reports say, about 70-80% of the anticancer drug molecules are derived from natural products such as plants (Newman & Cragg, 2016). Several plants have been identified to produce the anti-cancer compounds as their metabolites (Table 3). In general, the drug discovery method is very expensive and requires a lot of time. However, *in silico* drug discovery has been proved to be cheaper and less time-consuming in comparison to conventional *in vitro* and *in vivo* studies. *In silico* drug discovery involves the systematic implementation of software and databases to assist in the drug discovery and development process. The process also facilitates the predictions of the interaction of given drug molecules along with the target/ receptor (Ntie-Kang et al., 2014). Several in silico techniques have been developed for the development of a novel drug molecule. Techniques such as molecular docking and molecular dynamics simulation can generate accurate results in the interaction study between the drug molecules and their targets. The same technique is also used to discover potential anti-cancerous drugs from the plants (Balupuri et al., 2020; Chepkirui & Kagia, 2020; Prada-Gracia et al., 2016). The basic flow chart to the discovery process and application of bioinformatics methods have been shown in Figure 1.

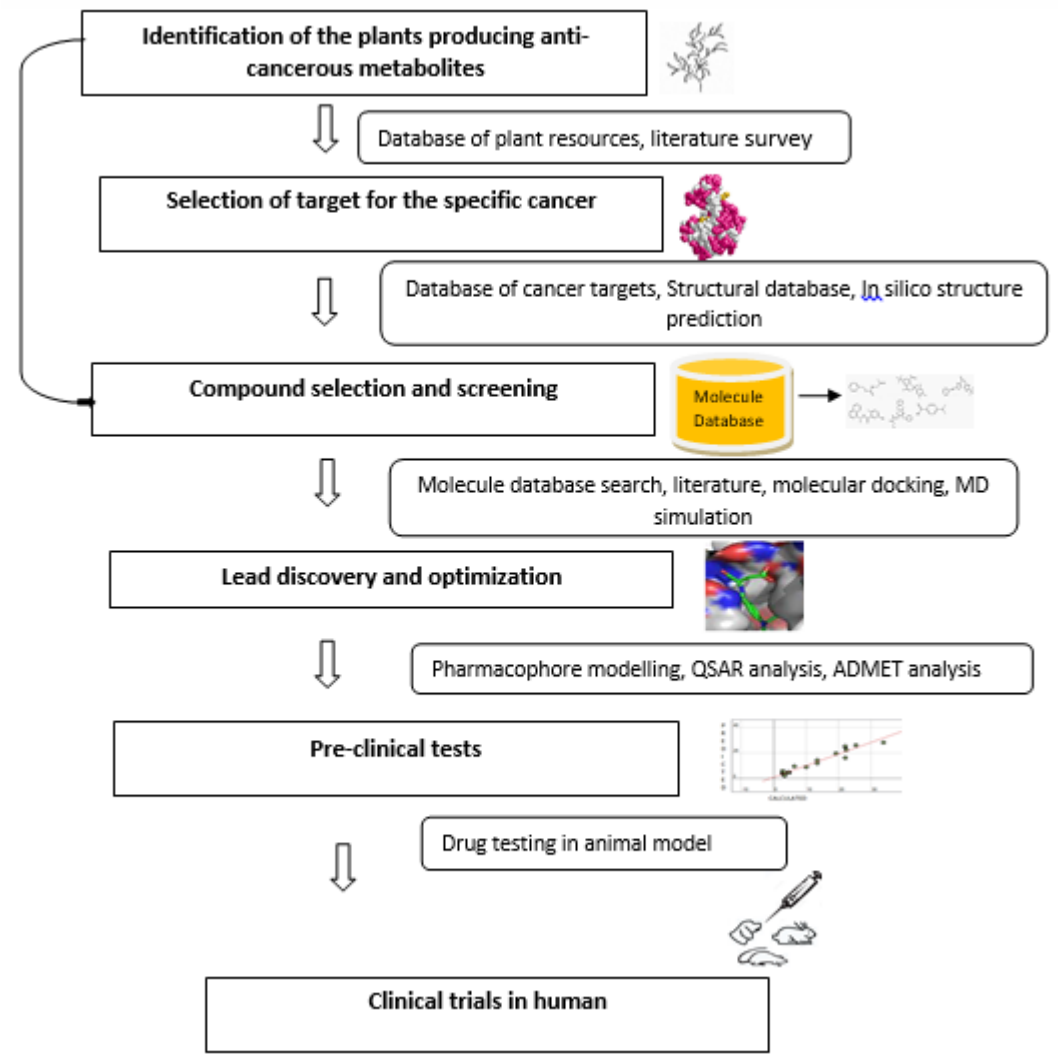
In general, the drug design process is a time-consuming process that involves a huge cost. The major objective of the drug design objectives is facilitated by the implementation of the Bioinformatics methods. Thousands of compounds are to be screened to obtain the most effective drug molecules that can be suitably applicable as an anti-cancer drug. The sophisticated computational methods have been

Table 2. Strategies followed to inhibit the cancerous cell

S. N	Inhibition/ Activation strategy	Pathways	Effect	References
1	Inhibition of angiogenic regulators	Angiogenic regulators are the signalling proteins in which binding of inhibitor causes inhibition of the function of cell surface receptors	Inhibition of angiogenesis process	(Baeriswyl & Christofori, 2009; Benouchan & Colombo, 2005; Bergers & Benjamin, 2003; Gutiérrez-Dalmau & Campistol, 2007; Hanahan & Weinberg, 2011; Neuzillet et al., 2015)
2	Inhibition of Proliferation signalling proteins	Proliferation signal inhibitors cause inhibition of cellular signalling pathways, hence exhibiting anti-neoplastic activity.	Deregulation of transforming growth factor-β (TGFβ) signalling pathway	(Gutiérrez-Dalmau & Campistol, 2007; Hanahan & Weinberg, 2011; Neuzillet et al., 2015)
3	Activation of Apoptosis process	Apoptosis (programmed cell death) plays a crucial role in the cell death of cancerous cells.	Activation of tumor necrosis factor (TNF), tumor-related apoptosis-inducing ligand (TRAIL) receptors, and other accessory factors to initiate apoptosis.	(Cotter, 2009; Fesik, 2005; Hassan et al., 2014)
4	Inhibition of Inflammatory targets	Inflammatory targets involved in the amplification of the inflammatory action, essential for the regulated cell growth, survival, migration, and invasion in cancer progression	anti-inflammatory agents/ drugs applied to inhibit the inflammatory pathways like NF kB, cytokine receptors, chemokine receptors, FGFR (Fibroblast Growth Factor/Receptor), cyclooxygenase (COX), and lipoxygenase (LOX) proteins	(Elinav et al., 2013; Koff et al., 2015; Schneider & Pozzi, 2011)
5	Inhibition of uncontrolled replication potential	As the replication of DNA is directly linked to the proliferation in the cancer cells. Hence, the inhibition of DNA replication in cancerous cells will act as the key element as a novel anti-cancer molecule	Inhibition of topoisomerase I and II	(Chhatriwala et al., 2006; Heck & Earnshaw, 1986; Järvinen & Liu, 2003; Kelland, 2007; Liu et al., 2013; Munster & Daud, 2011; Schiller et al., 2002)
6	Inhibition of hormone specific targets	Prolonged hormone exposure is associated with the risk of breast cancer	A class of targeted drugs that interfere with estrogen's ability to promote the growth of estrogen receptors (ER) ultimately causes the breast cancers	(Brusselmans et al., 2005; Chumsri et al., 2011; Hawkins et al., 1980; Pardee et al., 2009; Kelsey et al., 1993)
7	Inhibition of Metastasis	Secondary tumors, developed by the metastasis process are linked to the abnormal biochemical changes in the normal cell.	Drug molecules are developed for the inhibition of growth factor signaling and cell-cell adhesion study.	(Leber & Efferth, 2009)

used that play a crucial role in the modern era of drug discovery (Figure 1). The computational methods

Figure 1. basics bioinformatics application strategies used in plant-based anti-cancer drug discovery



can be applied successfully at almost all the steps of the anti-cancer drug discovery pipeline and are described in the below sections.

1. IDENTIFICATION OF CANCER DRUG TARGET

Usually, the drug target is a macromolecule that is essential for the cause of the disease, in which the drug molecule binds and biological activity is initiated. For the identification of the drug target, it is essential to understand the functional and structural aspects of the macromolecule. Several features such as prediction of the function of the molecule, metabolic pathway analysis and interactions details, disease-causing features and three-dimensional structural information are to be considered, during the identification and prediction of a drug target. The objective in drug development against the cancerous

Table 3. Some major online resources for anti-cancerous molecule from the medicinal plants

S. N	Resources	Availability	Remark
1	Indian Plant Anticancer Compounds Database (InPACdb)	http://www.inpacdb.org.	database of potential anticancer phytochemicals
2	NPCARE	http://silver.sejong.ac.kr/npcare	online database of natural products and plant extracts used for cancer control
3	CancerHSP	http://lsp.nwsuaf.edu.cn/CancerHSP.php.	records anticancer herbs related information through manual curation.
4	TIPdb	https://cwtung.kmu.edu.tw/tipdb	Searchable online database for phytochemicals of anti-Cancer, anti-Platelet, and Anti-Tuberculosis
5	Indian Medicinal Plants, Phytochemistry And Therapeutics (IMPPAT)	https://cb.imsc.res.in/imppat/home	A curated database of plants and their phytochemicals can be used for therapeutic strategies of many diseases including cancer.
6	Alkamid Database	http://www.alkam id.ugent .be	The database contains *N*-alkyl amides compounds producing plants, their biosynthetic pathways, and pharmacological importance.
7	Asian Anti-Cancer Materia Database	http://www.asian cance rherb .info/herbList/lists.htm	The database contains 700 types of plant-based anti-cancer drug information from Asia
8	CHMIS-C (A Comprehensive Herbal Medicine Information System for Cancer)	http://www.sw16.im.med.umich.edu/chmis-c	Contains 527 anti-cancer herb descriptions and 9366 small molecular structures that can be used for different types of cancer treatment
9	CNPD (Chinese Natural Products Database)	http://www.neotr ident .com/product/detail.aspx?id=16	contains more than 57,000 natural products including the features like the CAS number, name, molecular formula, and so on can be used as therapeutic molecules against diseases including cancer

cell leads to the inhibition and death of the cell. The net physiological effect of the drug binding activity should be studied so the side effects can be avoided. The experimental three-dimensional (3D) structure of the cancer target can be obtained from the protein data bank (PDB) database. However, in the absence of experimental structures, the protein modeling techniques (homology modeling, fold recognition, and ab initio prediction methods) can be implemented to derive the 3D structures of the target sequence information. Further, the binding site analysis of the target is to be analyzed, where the drug is going to bind (Cortés-Cros et al., 2013; Haley & Roudnicky, 2020; Manchado et al., 2016). As the cancer is concerned, the targets can be obtained from the specialized database available (Table 4)

2. MOLECULAR DOCKING

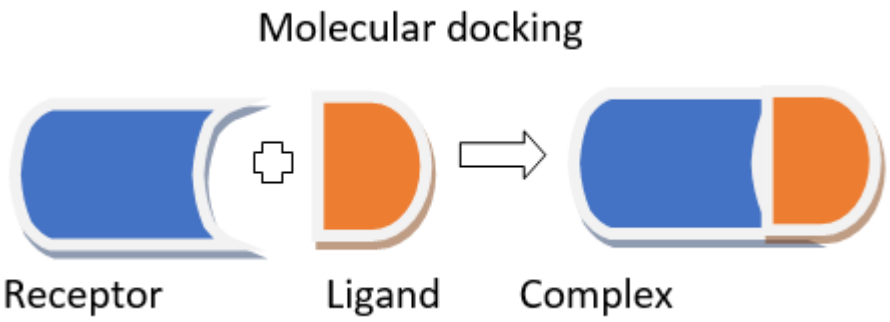
Molecular docking is a computational phenomenon in which the ligand (drug) binding affinity to its receptor (target) protein is evaluated based on binding energy and conformation of the ligand molecule

Table 4. Cancer target database

S. N	NAME	AVAILABILITY	APPLICATION
1	TARGET (tumor alterations relevant for genomics-driven therapy)	https://software.broadinstitute.org/cancer/cga/target	a database of genes, when altered by mutation causes the cancer
2	checkpoint therapeutic target database (CKTTD)	http://www.ckttdb.org/target.html	Checkpoint targets play a key role in tumor-mediated immune response
3	CancerResource	http://data-analysis.charite.de/care/	the database contains the mRNA expression and non-synonymous mutations data
4	Therapeutic Target Database (TTD)	http://db.idrblab.net/ttd/	A *database* to provide information about the known and explored *therapeutic* protein and nucleic acid *targets*, the *targeted* disease and cancer

(Figure 2). The computer programs involved in the docking process are categorized into two categories such as *flexible docking* and *rigid docking* as per the flexibility of the ligand involved in the process. (Dias et al., 2008; Morris & Lim-Wilby, 2008; Satpathy, 2020).

Figure 2. Showing the phenomena of molecular docking



The rigid docking method is based on the complementarity nature of physical, chemical and geometrical features between the ligand and the target proteins, but ignores the flexible property (both protein and ligand behaves as rigid molecules). But in the flexible docking method, usually, the ligand is flexible, and the receptor molecule behaves as rigid, hence the more accurate result is obtained, so this method is preferably used for the docking purpose. In the docking methods, the 3D structures of ligand and receptor molecules are to be obtained. Finally, these molecules are used in the docking programs to evaluate the binding energy. The docking programs use two types of algorithms to evaluate the binding affinity, the searching, and scoring algorithms (Fan et al., 2019; Gschwend et al., 1996; Shoichet et al., 2002; Yuriev et al., 2015). Several programs are available freely to perform molecular docking, given in Table 5.

Table 5. free academic programs of the docking program

S. N	Name of the program	Availability	Searching algorithm used
1	AUTODOCK4	https://autodock.scripps.edu/	Lamarckian genetic algorithm
2	DOCK	http://dock.compbio.ucsf.edu/	Shape matching
3	SWISSDOCK	http://www.swissdock.ch/	Evolutionary optimization
4	RDOCK	http://rdock.sourceforge.net/	hybrid
5	LEDOCK	http://www.lephar.com/software.htm	Simulated annealing
6	HADDOCK	https://wenmr.science.uu.nl/haddock2.4/	hybrid
7	IGEMDOCK	http://gemdock.life.nctu.edu.tw/dock/igemdock.php	Evolutionary algorithm

3. STRUCTURE AND LIGAND BASED PHARMACOPHORE MODELING

After molecular docking, it is important to predict the specific important molecular interactions between the ligand and receptor molecule. The term Pharmacophore modeling is used to interpret the essential electronic features available in the ligand molecules that enable a drug molecule to interact with the specific target receptor and it is related to the biological activity. In the past 10 years the pharmacophore mapping and modeling have been widely used in drug molecules, hence facilitating the accuracy in the process like virtual screening, lead optimization, and *de novo* drug design (Gilner et al., 2000; Yang, 2010). Based on the structural basis of the pharmacophore modeling two categories of analysis are performed such as ligand-bound type and without ligand bound type (only receptor) (Pirhadi et al., 2013). Table 6 presents some commonly available tools for pharmacophore modeling that can be used to identify the potential anti-cancer compounds (Table 6).

4. QSAR MODELING

Quantitative Structure-Activity Relationship (QSAR) is a computational modeling approach in which the different molecular features of the ligand are evaluated based on biological activities. In this technique, the drug molecule is subjected to the calculation of specific molecular descriptors (quantitative features taken as independent variables), and the biological activities (cytotoxic nature of the anti-cancerous drugs) are taken as a dependent variable. Further mathematical modeling is performed to predict the correlation between the two variables. Several molecular features such as two-dimensional and three-dimensional features related to them can be computed by using several (on-line) tools available. Similarly, various mathematical modeling methods are also available to find the correlation such as Multi Linear Regression (MLR), Artificial Neural Network (ANN), Support Vector Machine (SVM) and so on. (Polishchuk, 2017; Satpathy, 2019). Several research reports are available that use various plant compounds for the evaluation of anti-cancer activities by using the QSAR analysis. Scotti, et al, implemented the QSAR analysis to analyze the anti-cancer activity of the flavonoid and their analogous compounds derived from the plant secondary metabolites (Scotti et al., 2012). Alam, S., & Khan analyzed the (DNA) topoisomerase IIα inhibition activity of Xanthones are natural constituents of plants in the families Bonnetiaceae

Table 6. Showing the tools and their availability to perform the pharmacophore modeling

S. N	Name of the program	Availability	Application
1	ZINC Pharmer	http://zincpharmer.csb.pitt.edu/	free pharmacophore search software for screening of potential molecules from ZINC database
2	FLAP (Fingerprints for Ligands and Proteins)	https://www.moldiscovery.com/software/flap/	Identification of pharmacophoric fingerprints and widely used for the ligand -receptor interaction
3	PharmaGist	https://bioinfo3d.cs.tau.ac.il/PharmaGist/	Ligand-based pharmacophore detection.
4	Ligand Scout	http://www.inteligand.com/ligandscout/	Creation of three-dimensional (3D) pharmacophore models from macromolecular structural data
5	Cavity Plus	http://www.pkumdl.cn:8000/cavityplus/index.php	protein cavity detection and functional pharmacophore analysis by the input of a 3D structure
6	Pharmit server	https://pharmit.csb.pitt.edu/	Molecular-level observation of pharmacophore
7	PMapper	https://github.com/DrrDom/pmapper	representation of 3D pharmacophores
8	PharMD	https://github.com/ci-lab-cz/pharmd	automatically retrieve the pharmacophoric features from MD simulation trajectories of protein-ligand complex

and Clusiaceae by the QSAR analysis followed by molecular docking methods (Alam & Khan, 2014). Alam, S., & Khan, F. also implemented structure-activity relationship for triterpene maslinic acid and its analogs to deduce the breast cancer inhibition of these compounds by taking experimental activity of these compounds as the dependent variables (Alam & Khan, 2017). Satpathy et al. studied the anti-cancer activities of the boswellic acids (derived from the plant *Boswellia Serrata*) by using quantitative structure-activity relationship (QSAR) models by using 2D descriptors (Satpathy et al., 2015). Sharma et al. studied the cytotoxic nature of flavonoids such as orientin and vicenin from the O. sanctum L by using QSAR analysis by taking the liver cancer cell line (Sharma et al., 2016). Miladiyah et al., conducted the study, by taking a series of xanthone derivatives and the cytotoxicity behaviours of the molecules were evaluated against the WiDR cell line (colorectal cancer). Further docking study suggested that the inhibition mechanism is due to the inhibition of the signalling process of cancer cells such as CDKase (cyclin-dependent kinase), telomerase, and tumor promoting inflammation pathways (Miladiyah et al., 2018). The software tools used for QSAR analysis and implementation has been given by discussed by Satpathy R, and some of the important computational tools used for QSAR analysis has been presented in table 7 (Satpathy, 2018).

5. MOLECULAR DYNAMICS SIMULATION TO FIND NEW ANTI- CANCER DRUG BINDING SITES

Molecular dynamics (MD) simulation is a computational technique in which the complex physical movement of the receptor (along with the ligands) can be understood. Since the binding of a drug molecule

Table 7. List of commonly used software tools used for QSAR study

Sl. No.	Simulation software	Availability
1	Molecular Operating Environment (MOE)	https://www.chemcomp.com/MOE-Cheminformatics_and_QSAR.htm
2	BIOVIA QSAR Workbench	http://accelrys.com/products/collaborative-science/biovia-qsar-workbench/
3	VEGAHUB	https://www.vegahub.eu/
4	WEKA	https://www.cs.waikato.ac.nz/ml/weka/
5	DTC-QSAR software	http://teqip.jdvu.ac.in/QSAR_Tools/
6	BuildQSAR	https://www.profanderson.net/files/buildqsar.php
7	DPubChem	www.cbrc.kaust.edu.sa/dpubchem
8	BioPPSy,	https://sourceforge.net/projects/bioppsy/.
9	CORAL software/	http://www.insilico.eu/coral/
10	QSAR-Co-X	https://github.com/ncordeirfcup/QSAR-Co-X
11	E-dragon	http://www.vcclab.org/lab/edragon/
12	PreADMET	https://preadmet.bmdrc.kr/

and the stability also influence the biological activity, hence time frame of this interaction is important to study. The basic objective of the molecular dynamics simulation is to provide a computer-based experimental setup to the receptor and ligands by which several microscopic molecular features such as the extent of stability of the ligand, energy profile, compactness of the protein, C alpha root mean square deviation and other molecular interaction phenomena can be studied. In this technique, starting from the macromolecular structures specific force fields are used to compute different properties from the MD simulation (Allen, 2004; Hollingsworth & Dror, 2018; Ponder & Case, 2003).

Jabbarzadeh Kaboli et al., studied the molecular dynamics simulation to evaluate the effectiveness of the plant-derived compounds berberine and their structural derivatives as the potential inhibitor of BRAF protein (Jabbarzadeh Kaboli et al., 2018). Aliebrahimi et al. studied some of the potential phytochemicals as the anti-cancer compounds by docking with c-Met receptor tyrosine kinase proto-oncogene by the docking followed by molecular dynamics simulation (Aliebrahimi et al., 2018). Recently, Gurung et al.

Table 8. List of some software tools used for MD simulation study

Sl. No.	Simulation software	Availability
1	GROMACS	https://www.gromacs.org/
2	NAMD	https://www.ks.uiuc.edu/Research/namd/
3	HYPERCHEM	http://www.hypercubeusa.com/
4	YASARA DYNAMICS	http://www.yasara.org/products.htm#dynamics
5	AMBER	http://ambermd.org/
6	MDWeb	https://mmb.irbbarcelona.org/MDWeb/
7	CABS-flex	http://biocomp.chem.uw.edu.pl/CABSflex/about.php
8	Ascalaph Designer	http://www.biomolecular-modeling.com/Ascalaph/Ascalaph_Designer.html

used molecular docking and MD simulation strategies to evaluate the binding affinity of plant-based active constituents with the anticancer drug target receptors such as cyclin-dependent kinase 2 and 6, topoisomerase-I and II, B-cell lymphoma 2 (Gurung et al., 2021). Ali, M. A. analyzed the cytotoxicity nature of '3,5,7,3′,5′-pentahydroxy-flavanonol-3-O-α-L-rhamnopyranoside from the v plant against the cancerous cell by using molecular docking and 40 nanosecond molecular dynamics simulation study (Ali, 2020). Mahmud et al. implemented molecular docking followed by MD simulation methods to study the plant-based compounds fraxoside, scopolin, and xanthone as the potential inhibitor of Carbonic anhydrase IX (hCAIX), an enzyme the overexpression of which lead to the cause of different cancers (Mahmud et al., 2021). Oyebamiji et al., studied some of the novel compounds of the plant *Annona muricata L as the inhibitor of 3α*-hydroxysteroid dehydrogenase (3*α*-HSD) to investigate the anti-cancer activity by using molecular docking, QSAR, and MD simulation analysis (Oyebamiji et al., 2020). Pandya et al., in their work, analyzed computational techniques such as molecular docking and Md simulation to discover the anti-breast cancer nature of the compound Subtrifloralactone G, derived from the plant *Deprea subtriflora*. Molecular docking of the compound with ABCC6 protein, followed by molecular dynamics simulation of the complex and ADMET analysis was used to establish the anti-cancer property of the compound (Pandya et al., 2020).

6. ADMET PROFILING

One of the most important parts of the anti- cancer-based drug development is Adsorption, Distribution, Metabolism Elimination, and Toxicity (ADMET) analysis. This is performed to check the proper pharmacokinetic property associated with the selected compound. This computational method is used to analyze the absorption and distribution of the drug molecule to the site of action. So that the drug should not be left with any trace in the body, so that it may lead to any adverse effect. In addition to this, the toxicity of the drug molecule is also evaluated to establish the compound as the potential anti-cancer compound (Davis & Riley, 2004; Ferreira & Andricopulo, 2019). Several computational online tools and pipelines are available for the prediction of the ADMET profile of drug molecules (Table 9).

Challenges in Discovery of Anti-Cancer Drugs

Although the implementation of the standard methods seems to be easy to discover a drug molecule against cancer, however in practice, it encounters huge challenges, discussed by many researchers (Celebi et al., 2019; Cui et al., 2020; Hoelder et al., 2012; Housman et al., 2014; Jean-Quartier et al., 2018; San Lucas et al., 2014). (Gilner et al., 2000; Kumar & Kumar, 2013; Safarzadeh et al., 2014; Schneider & Pozzi, 2011; Zugazagoitia et al., 2016)

Although the implementation of the standard methods seems to be easy to discover a drug molecule against cancer, however in practice, it encounters huge challenges, discussed by many researchers [90-95].

- The estimated number of the types of cancer is about 200, based on the histological/ anatomical position of the body they occur; hence, a specific inhibitor molecule is to be developed as per the class of kinase (target) protein present in that part of the body.

Table 9. Showing the computational resources for ADMET prediction

S. N	Tool	Availability	Remark
1	ACD/PhysChem Suite	https://www.acdlabs.com/products/percepta/	Prediction of Physico-chemical, ADME and toxicity prediction
2	ADMET Predictor	https://www.simulations-plus.com/	Prediction of ADMET properties by the input of 2D structure of compounds.
3	AMBIT	http://cefic-lri.org/toolbox/ambit/	database integrates models for toxicity prediction
4	ADMETlab 2.0	https://admetmesh.scbdd.com/	Evaluates the ADMET properties, physicochemical properties
5	vNN-ADMET webserver	https://vnnadmet.bhsai.org/vnnadmet/login.xhtml	Prediction of ADMET properties and generates new models based on variable nearest neighbor (vNN) methods.
6	SwissADME	http://www.swissadme.ch/	Used to compute various features such as physicochemical descriptors, ADME parameters, pharmacokinetic properties, drug likeness and so on.
7	pkCSM	http://structure.bioc.cam.ac.uk/pkcsm	Development of predictive models for ADMET properties in the drug development process
8	admetSAR	http://lmmd.ecust.edu.cn/admetsar2/	Open source database used for structure-activity relationship of molecules and predicts the ADMET and related properties

- The presence of thousands of numbers of genetic alternations/mutations present in the individual cancer cell types is another challenge, hence the developed drug molecule may not be able to recognize the target.
- The approaches of combined therapy for the multi-target treatment of cancer also have limitations as the simultaneous administration of drug molecules might result in a lack of interaction among the drugs may lead to cause toxic effects.
- Although a large number of effectively predicted drug molecules are available, their activity towards the receptor-containing mutation and specific cancer-based biomarkers has not been established yet.
- Especially for cancer, selection and validation of the target is a difficult task and challenging as it is associated with a complex biochemical signalling process.
- Further, after the identification of a potential novel drug molecule, the effectiveness of the molecule in clinical trials is uncertain.
- In addition, the resistance mechanism of the cancerous cell may lead to a reduction in the level activation of the drug

CONCLUSION

Currently, the increase in the number of cancer patients throughout the world creates a public health challenge. Due to various types of cancer as per the occurrence in the body, it is difficult to diagnose as well as to formulate a specific treatment process. Also, as per the WHO information, cancer is consid-

ered to be one of the significant causes of death in recent times. In these aspects, novel drug discovery plays a major role to treat the disease. Traditional approaches adopted for drug discovery against cancer are based on animal experiments (*in vivo*) as well as the process of drug screening (*in vitro*). However, these methods are expensive and time-consuming. In recent times, Bioinformatics based methods are widely used to discover, analyze and validate potential anti-cancer agents. Plants act as a major repository for novel anti-cancer agents. Many of the plant metabolites has been scrutinized and evaluated as potential candidate to treat cancer by using sophisticated bioinformatics tools. In this chapter, basic computational strategies that are being adopted in the discovery of new anti-cancer compounds from plant sources have been discussed. Also, the computational methods, resources, and their availability and applications have been discussed by taking suitable examples from the literature. In addition to the traditional computational resources, a new complex plant product-based cancer information dataset is to be developed. Further analysis with advanced computational tools encrypted with the improved algorithms may generate suitable therapeutic options for the cancer patient.

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