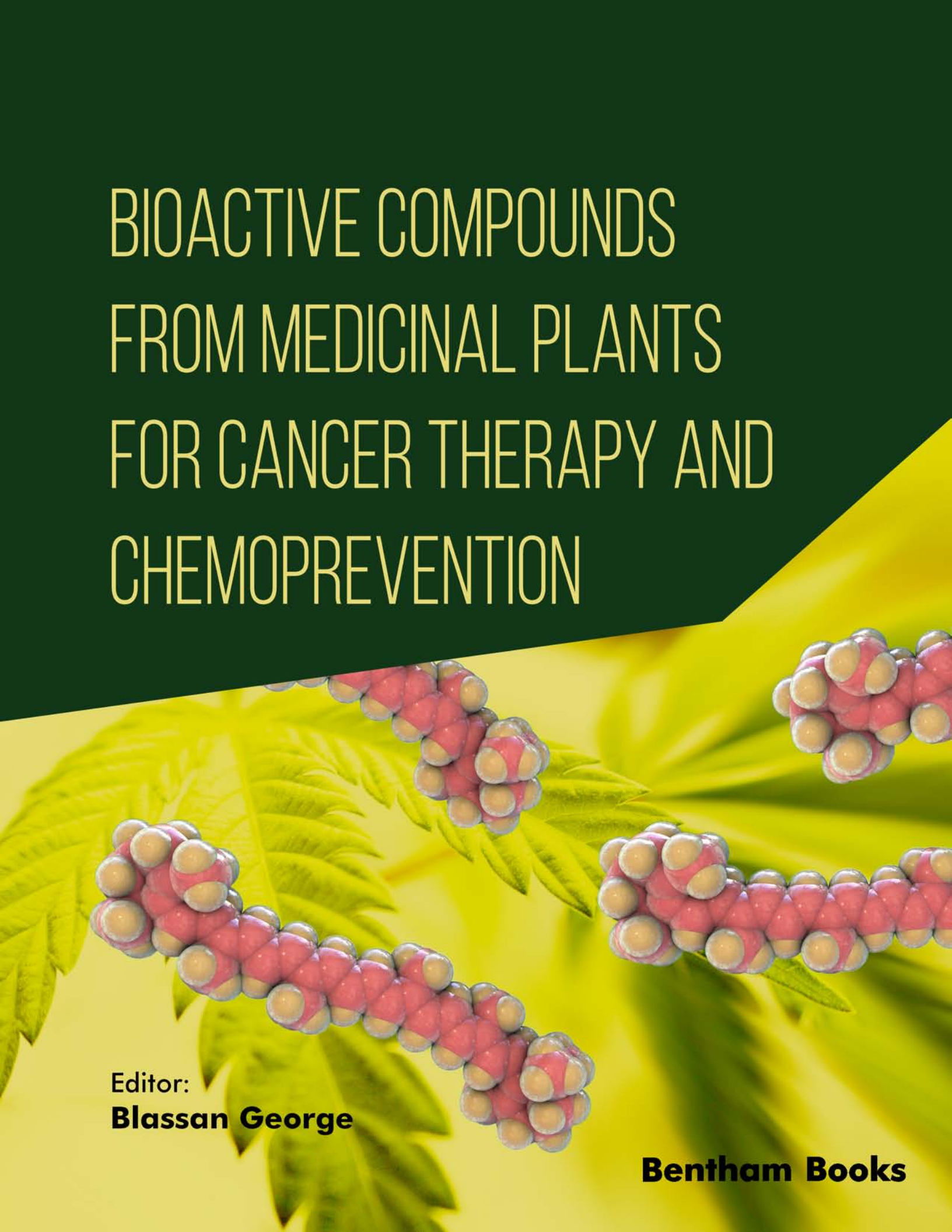
# BIOACTIVE COMPOUNDS FROM MEDICINAL PLANTS FOR CANCER THERAPY AND CHEMOPREVENTION



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# Bioactive Compounds from Medicinal Plants for Cancer Therapy and Chemoprevention

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# PREFACE

Research on medicinal plants is one of the most important areas in oncology with high potential in the design and development of cost-effective drugs. Natural products in the treatment of diseases have been practiced since ancient times. Cancer chemoprevention is a broad term that uses synthetic and natural compounds to slow down, suppress or reverse carcinogenesis. The onset of cancer depends on various factors such as intrinsic and extrinsic. Natural therapies, such as the use of plant-derived products and medicinal plant extracts in cancer treatment, may reduce the adverse side effects of conventional treatments. The cancer control measures are related to the origin and risk factors. Every cancer type needs specialized therapy, and the most important treatment goal is to eradicate tumour and prolong the patients' lifespan. Alternative therapies have been playing a crucial role in cancer treatment and management. Several studies reported that medicinal plants and bioactive compounds from plants can work well as an alternative cancer treatment option for different types of cancers due to fewer side effects and cost-effectiveness compared to many existing treatments. Phytochemicals from medicinal plants were reported to reduce various risk factors associated with cancer through their chemopreventive action. This book highlights the role of bioactive compounds and dietary factors or natural products from plants or medicinal plant extracts in the chemoprevention of various types of cancer. Since the role of antioxidants in chemoprevention is unavoidable, an insight into plant-based antioxidant compounds that fight against cancer is also discussed in this book. Medicinal plants, bioactive compounds derived from marine sources, and the role of antioxidants in cancer therapy and chemoprevention, and molecular mechanisms in clinical trials are included in this book. This will fill the research gap in search of chemopreventive natural compounds and encourage researchers to produce anticancer agents from plants in clinical trials.

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# CHAPTER 1

# Role of Antioxidants in Cancer Therapy and Chemoprevention

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**Abstract:** Malignant diseases have been highlighted as one of the most prominent causes of human mortality worldwide. The prevalence of cancer is constantly increasing and is expected to reach three-fourths of the population in the next two decades. Conventional cancer treatment involves surgery, controlling and reducing the growth of cancer tissues using radiation, and chemotherapy. Many incidences prove that chemical treatment for cancer is immensely associated with the recurrence of cancer, and the development of resistance, and is prone to severe side effects. Since natural products have now been used in the treatment of various diseases, the anticancer properties of natural drugs and druggable products are interceded by various mechanisms, including the initiation of programmed cell death, modulations in the immune system, and inhibition of angiogenesis. Edible, medicinal plants and spices used in traditional medicine to regulate vital molecular targets are important chemo-preventive agents in the treatment of chemo and radiation therapy-induced toxicities in drug development. Natural agents could trigger cell death signalling pathways in tumour cells by stimulating anti-apoptotic proteins and/or overcoming pro-apoptotic proteins and caspases. It inhibit protein kinase B (Akt), phosphatidylinositide 3-kinases (PI3K), epidermal growth factor receptor/mitogen-activated protein kinase (EGFR/MAPK), as well as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Bax/Bcl-2 ratio changes, inhibiting cellular proliferation, and differentiation, and also activating apoptosis lead to less prominence. To summarize, this chapter highlights the current status, and forthcoming prospects of cancer treatment and prevention as well as the potential of bioactive compounds that have been used in cancer treatment and chemoprevention.

**Keywords:** Antioxidants, Bioactive compounds, Free radicals, Molecular targets and chemoprevention.

## INTRODUCTION

Cancer is a life-threatening disease and a prominent cause of death globally [1], and is probable to rise in the next 2 decades. Generally, it is assessed that the total

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cancer prevalence could extend up to 2.84 crore in 2040 [2]. Oxidative stress induced by free radicals is usually found in physiological and metabolic processes and the human body has a defensive system of antioxidant mechanisms; these include enzymatic antioxidants *e.g*., superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) as well as natural antioxidants such as vitamins, carotenoids, polyphenols, and other antioxidants, which have the potential to neutralize free radicals [3]. Henceforth, research has been directed towards therapeutic plants and the promising potential of such plants in various traditional and alternative medicine systems for use in humans has been valued. The secondary metabolites are measured as good chemopreventive agents and can be used for cancer therapy due to the high concentration and a wide variety of natural antioxidants such as resveratrol, vitamins, flavonoids, polyphenols, and other compounds found to influence different cancer cells both *in vitro* and *in vivo*. As an antioxidant network, these natural antioxidants also have efficient synergistic interactions and renewing prospects [4]. Though huge advances have been made in research focusing on the etiology and molecular substructures of cancer, the treatment for cancer has severe side effects that limit patients' quality of life.

Hence, it is a matter of life and death to intend processes to diminish cancer occurrence or inhibit the development of cancer to its advanced stage. The knowledge of chemical prevention is acquired with more concern comparatively due to its success in reducing the frequency of metabolic disorders and heart diseases.

Chemo preventives can be classified based on the point at which they perform as primary, secondary, and tertiary groups. Primary chemopreventive are aimed at suppressing the incidence of cancer formation in a predisposed metabolism. Secondary chemical prevention agents overwhelm the evolution of cancer prevalence from non-dangerous (benign) to dangerous (malignant). Tertiary chemical prevention agents lower the risk of tumour reappearance following a suitable treatment like incision and/or chemotherapy [2]. Among several kinds of cancer chemo preventive agents, hormonal and vaccines are recorded as more promising means for future research and therapeutics. In addition, individuals who have benefitted from chemical prevention due to their hereditary advantages give diverse interpretations for the efficient assessment of cancer chemotherapy [5].

## ANTIOXIDANTS AND TREATMENTS IN CANCER THERAPY

The metabolic trembling molecules acknowledged as free radicals have damaged the other molecules. In presence of oxidative stress, these free radicals develop

cancer and a chain of reactive oxygen species. Antioxidants play a vital role in plants' and animals' nutrition because they react with these free radicals, which soothe and quench them. Natural antioxidants from plants including vitamins C, E, and A, curcumin, beta-carotene, kaempferol, and quercetin assure that the systematic intake of fruits and vegetables has consistently reduced not only the risk of cancer incidence but also other diseases like Cardiovascular disease, Diabetes, Alzheimer's disease, *etc*. [6].

In recent years, neoplasm medicine research has taken significant steps towards additional efficiency, specifically invasive cancer treatments. Nanomedicine combined with directed treatment aided in recovering the bio-distribution of novel or existing chemotherapeutic agents. Other approaches like gene therapy, siRNA delivery, immunotherapy, and antioxidant supplements provide new prospects for malignancy victims. In contrast, hyperthermal or hypothermal treatments are favourable substitutes and personalised medicine for tumour excision. Additionally, recent radiomics and pathomics methods for the management of big data sets from cancer patients to recover and predict cancer recurrence and related effects on their health [7].

Most of the novel therapies, including nanomedicine are flexible and safe for the living tissues and environment and can deliver chemotherapeutic drugs that can also be used with diverse applications from diagnosis to treatment [8]. Extracellular vesicles play a significant role in apoptosis and are explored as a proficient remedy in cancer therapy. Plant-derived antioxidants and numerous bioactive compounds have been recently used as adjuvant cancer treatments with pro-apoptotic properties. Gene therapy targets genes that trigger cancer suppressors and tumor suppressors that have been valued and tested in many clinical trials worldwide [9]. These approaches are the best-adapted treatments for cancer sufferers and the prominence of multi-disciplinary approaches to attain the desirable effects as proved in various clinical experiments. Cancer treatments and newly anticipated approaches that are in the investigation phase should overcome the constraints of cancer. Diverse strategies for cancer diagnosis, treatment and addressing existing consequences from the scientific perspectives and causal impacts of natural agents are required to approach the disease closer [10]. Though much debate has arisen about the efficiency of cancer chemotherapy, inadequate substantiation has been observed in both the quality and dose of antioxidants, which suggests that they may reduce antagonistic responses and harmfulness [11]. It is indicated that researchers' effort to explore alternate composition and treatment methods to reduce persistence, growth and multiplication, transference of cancer cells, and development of blood vessels [12] and the interface of chemical treatment and antioxidants is more complicated than merely preventing

CHAPTER 2

# Medicinal Plants and Cancer Chemoprevention

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**Abstract:** Cancer is identified as the second-most deadly disease all over the world. Various advancements have been made in the treatment of cancer to protect the life of human beings. However, the side effects may destroy the lives of the patients. Economically poor patients cannot afford the treatment, and they live short lives with cancer. So nowadays, research is going on to search for drugs without any side effects and that are cheap with good efficacy. Some medicinal plants have a lot of potential to act as anticancer agents but are not medically proven as discussed in this chapter. This review will focus on the various plant-derived chemical compounds that have shown anticancer activity.

**Keywords:** Anaferine, Anticancer activity, *Annona Muricata* L., Bullatacin, *Camptotheca acuminata*, *Catharanthus roseus*, Chemoprevention, Isopelletierine, Medicinal plants, Natural products.

## INTRODUCTION

Cells are the basic and small units involved in the construction of our body. The regular activity of a cell is to grow itself, and after sometime, it will fracture or break itself. This process is known as cell replication. When this regular activity becomes abnormal, it results in cancer. These types of abnormalities are inferred due to repaired DNA in the cells. There are many ways to affect the DNA of cells. Environmental activities can damage the cellular DNA. During cell growth and replication, there will be a chance to cumulate and form tumours. In this way, tumours degrade or damage the nearby healthy cells [1].

Cancer is considered the second-most deadly disease. The main reason for cellular DNA damage is lifestyle change, which is why researchers are focusing on finding new chemotherapeutic agents that are economically favourable to society. According to the survey report given by the WHO, in 2012, only 6 million people recovered from cancer out of 14 million. This is the financial barrier faced by the

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affected people [2]. Even though different types of cancer are present, breast cancer is mostly and frequently identified among females [3, 4]. Colorectal cancer is considered the third most common cancer in the world. It is expected that it will become 60% malignant by the year 2030 [5].

## TYPES OF TREATMENT FOLLOWED FOR CANCER

It depends on the stage of the disease, and the type of treatment chosen.

I. Surgery,
II. Radiation therapy,
III. Chemotherapy,
IV. Biological therapy,
V. Hormone therapy

the above-mentioned treatments have advantages and disadvantages. When the combination of any two of the above is followed to get effective results, there is a chance to get immediate negative responses. In case of surgery, normal cells are triggered to become metastatic cancer cells. After the successful removal of the tumour, sometimes the patient dies due to the side effects.

From 1950 onwards, chemotherapeutic agents were used to control the growth of cancer cells or even destroy cancer cells. These agents, along with some physical practices, may cure specific cancers. In other types, it may extend the lifetime of the patient without a complete cure [6].

## ADVERSE EFFECTS OF CANCER TREATMENTS

The major effects of chemotherapy and radiation therapy are nausea, vomiting, and fatigue. Other side effects are hair loss, appetite loss, changes in taste, *etc.* There is a chance for a second cancer after chemotherapy, and it may affect other organs like the kidneys, lungs, heart, *etc.*, and may cause nerve and psychological problems [7, 8].

## ADVANTAGES OF HERBAL DRUGS OVER ALLOPATHIC DRUGS IN CHEMOPREVENTION

Due to the side effects of allopathic drugs, research is focused on natural products. Most of the anticancer drugs are derived from plants like taxane, vinca alkaloids, podophyllotoxin, and camptothecin [9]. Herbal practitioners can easily identify cancer and use herbs for different cancers. Especially, breast cancers are most frequently treated by herbalists [10].

For instance, a total of 151 medicinal plants were reportedly used to treat various types of cancer, such as breast, liver, prostate, stomach, and brain, by traditional herbs in the Ashanti region of Ghana. These included *M. Charantia, B. pinnatum, X. aethiopica, H. indicum, Z. officinale, A. melegueta, A. comosus, E. heterophylla, M. indica, K. africana, A. muricata, E. guineensis,* and *P. guajava* that are discussed in the present study [11].

Medicinal plants continue to play a central role in the healthcare system for large proportions of the world. Recognition and development of the medicinal and economic benefits of plants are on the increase in both developing and industrialised nations. An herb (also called a botanical) is a plant or plant part used for its scent, flavor, and/or therapeutic properties. Products made from botanicals that are used to maintain or improve health have been called herbal supplements, botanicals, or phytomedicines. The pharmacological treatment of disease began long ago with the use of herbal medicines, which are "crude drugs of vegetable origin utilized for the treatment of disease states, often of a chronic nature, or to attain or maintain a condition of improved health,". Herbal medicines can also be defined as "finished labelled medicinal products" that contain ingredients from aerial or underground parts of plant parts or other plant materialsor combinations in the crude state or as plant preparations. It has been estimated that these medicines derived from plants constitute about 25 percent of modern pharmacopoeia. In this chapter, we are going to learn about some medicinal plants and their role in cancer cells.

## PLANTS WITH TREMENDOUS ANTICANCER ACTIVITIES

### *Catharanthus Roseus*

Common names of *Catharanthus roseus*, are Bright Eyes, Old Maid, and Pink Periwinkle. It comes from the Apocynaceae family. The plant is displayed in Fig. (**1**). The drugs named Vincristine and vinblastine, Vindesine, Vindoline, and Tabersonine are used in cancer treatment, and these are derived from *Catharanthus roseus* [12]. More than 100 monoterpenoids and indole alkaloids are present in this plant. Vincristine is also used to treat leukaemia in children. In previous years, this plant has been used as a muscle pain reliever, relieving depression in the central nervous system, and for treatment of nose bleeding, and gum bleeding [13]. It contains non-enzymatic and enzymatic antioxidants [14, 15]. Whereas ajmalicine, vinceine, vineamine, raubasin, reserpine, catharanthine, *etc.* are present in roots and basal stems and are shown in Fig. (**2**) [16].

# CHAPTER 3

# Bioactive Compounds Derived from Marine Sources for Cancer Therapy and Chemoprevention

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**Abstract:** The relatively unexplored marine environment is a rich resource of novel bioactive candidates that may be beneficial for human beings. Since the marine environment is complex in nature, living organisms produce secondary metabolites with unique biological properties that could find applications in health care systems. This chapter gives an overview of marine-based anticancer drugs that are FDA-approved and bioactive components that are under preclinical and clinical trials. It also provides insight into marine-based nutraceuticals, their sources, and their usefulness for various human health concerns. Therefore, exploring the marine environment through collaborative research work both by academia and industries could lead to significant contributions to humanity.

**Keywords:** Anticancer drugs, Clinical, Marine resources, Nutraceuticals, Preclinical trials.

## INTRODUCTION

Since the emergence of human beings, natural products have been used to treat various diseases. In particular, natural products derived from plants contributed to more than 60% to the development of traditional medicine systems. Their roles in the healthcare system had been well documented by different cultures, including Indians, Chinese, Egyptians, Romans, *etc.* World Health Organisation (WHO) has estimated that 65% of the world's population depends on plant-based traditional

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medicines for their primary health care [1]. As we are all aware cancer is a dreadful disease caused by uncontrolled and abnormal cell growth, these cells have the potential to kill normal cells and spread easily to all parts of the body. There are more than 100 different kinds of cancer that affect human health dreadfully worldwide.

The main causes for this disease are the excessive use of tobacco, poor diet, obesity or overweight, and exposure to radiation. However, certain kinds of cancer can be prevented if diagnosed in the early stage, which include breast, cervix, colon, rectum, skin and prostate cancers. Common treatment methods employed for cancer include surgery, radiotherapy and chemotherapy. Most of the cancer treatments depend mainly on chemotherapy. It is a form of treatment based on drugs that interfere with the progression and division of tumour cells. However, most chemotherapeutic drugs lack selectivity, and cause immunity suppression and other side effects such as hair fall, kidney failure, and nausea. Hence, there is a worldwide impetus to develop chemotherapeutic drugs to overcome these side effects.

Natural products derived from plant sources like vinblastine, vincristine, etoposide, and podophyllotoxin have been effectively used in the treatment of cancers [1]. Despite the vast expanses of the Earth's surface covered by oceans, amounting to 70%, and the plethora of organisms inhabiting these waters, contributing to an immense chemical diversity, the exploration of natural products derived from marine sources remains significantly underexplored. The ocean is one of the treasures of natural products that can be obtained from various species, such as microalgae, fungi, bacteria, sponges, tunicates, seaweeds, *etc*. Marine organisms produce secondary metabolites during their activities, such as defence, competition, communication, and predation. These metabolites were once considered wastes but are now potential compounds having applications in various fields such as pharmaceuticals, cosmetics, and nutritional supplements. These metabolites mainly consist of terpenoids, alkaloids, sugars, steroids, polyketides, peptides, shikimic acid derivatives, and various kinds of mixed biogenesis metabolites [2]. Table **1** depicts the compounds under different classes showing potential bioactivity. Currently, about 30 marine-based compounds are in different phases of clinical trials that may be employed as potential medicines for treating different types of cancer. In this section, some of the marine-based bioactive molecules that are used in the treatment of cancer and also used as dietary supplements (Nutraceuticals) to prevent certain diseases will be discussed. In addition to this, this chapter shines light on the marine-derived bioactive molecules that are in different phases of clinical trials for the treatment of cancers.

**Table 1. Different classes of compounds showing biological activity derived from marine sources.**

| Chemical Class | Compounds Included | Pharmaceutical/Biological Activity | Anticancer Chemicals | Marine Sources |
|---|---|---|---|---|
| Alkaloids [3] | Pyridoacrines;indoles; pyrroles; isoquinoline; gaudinines; aminoimidazoles; and sterols. | Antifouling; cytotoxic; anticancer; antimalarial; and antimicrobial. | Topsentin; tambjamine D; Spongiacidin C; and discohabdines. | Sponges; tunicates; anemones, and mollusks. |
| Polyketides [4] | Macrolides; polyethers; polyols; and aromatic compounds. | Antibiotic; anticancer; antifungal; antiparasitic, and neurotoxic effects. | Haloroquinone; SZ-685C | Sponges; ascidians; Soft corals and bryozoans, and commensal or symbiotic bacteria. |
| Polyphenols [5] | Phenolic acids; flavonoids; anthocyanidins; lignin; tannins; catechin; epicatechin; epigallocatechin, and gallic acid | Antioxidant; anticancer; antiviral; anti-inflammatory; inhibit human platelet aggregation; metal chelators. | Scutellarein 4'-methyl ether; phloroglucinal; ecol; phlorofucofuroecol A; diecol, and 8,8'-Biecol | Seaweeds; seagrass, and mangroves. |
| Terpenes [6] | Monoterpenes; sesquiterpenes; diterpenes; sesterterpenes; triterpenes (steroids), and tetraterpenes (carotenoids) | Cytotoxic; antiproliferative; antifouling; anticancer; antifungal, and antimicrobial. | Caulerpenyne; usneoidols Z and E | Soft coral and sponges. |
| Peptides [7] | Cyclic depsipeptides Mirabamides; papuamides; celebesides; theonellamide; pipecolidepsins, and various others | Cardiotonic; antiviral and anticancer; cardiotoxic and antimicrobial. | Brugine, and benzoxazolinone | Sponges; commensal or symbiotic bacteria or fungi. |

# CHAPTER 4

# Bioactive Compounds in Cancer Therapy and Chemoprevention

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**Abstract:** The continuous increase in the number of cancer cases and rates of cancer-related mortality globally is a highly concerning issue. Drug-induced toxicity, drastic side effects and chemoresistance associated with conventional chemotherapeutics warrant the need for novel, efficient, and safer alternative therapeutic approaches to help combat cancer. Plants are a rich source of bioactive compounds with potential anti-cancer activity. Extensive research on the chemotherapeutic efficacy of various plant-derived bioactive compounds is being carried out across the world. While cancer chemoprevention approaches prevent, delay, or suppress tumor incidence, chemosensitization approaches employ synthetic or natural bioactive agents to enhance the efficacy of conventional chemotherapeutic drugs at lower doses. Numerous studies have documented the efficiency of both of these approaches in managing different types of cancer. The scope of this chapter encompasses a comprehensive analysis of the current status and limitations of conventional chemotherapeutics and the clinical relevance of chemoprevention and chemosensitization strategies for the effective management of cancer, with a special emphasis on the potency of some of the major phytochemicals that are extensively being studied as novel chemopreventives and/or chemosensitizers, globally. Besides, an overview of the underlying mechanisms of action of these phytochemicals in regulating the signal transduction events associated with cancer progression, has also been discussed in this chapter.

**Keywords:** Bioprospecting , Chemoprevention , Chemoresistance , Chemosensitization , Chemotherapeutics , Phytochemicals .

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## INTRODUCTION

Cancer is one of the primary causes of mortality across the world. Over the past few decades, there has been an incessant rise in the rates of cancer incidence as well as in the rates of cancer-related deaths, globally. According to GLOBOCAN Report 2020, cancer accounted for approximately 10 million deaths out of around 19.3 million cancer cases worldwide in the year 2020 and these figures are estimated to escalate up to 28.4 million cases by the year 2040 [1, 2].

By definition, cancer refers to an array of neoplastic diseases that originate in almost any tissue or organ of the body, in which abnormal cells divide uncontrollably and invade nearby tissues as a consequence of aberrant signalling pathways and accumulation of genetic mutations [3]. Initiation and malignant progression of cancer occurs in multiple stages. The initiation of cancer starts with the genetic mutations, which help cells to resist cell cycle control. This is followed by the uncontrolled cellular proliferation, evasion of apoptosis and immune response, altered energy metabolism and development of vasculature *via* angiogenesis in cancer cells, which aid them in their uncontrolled growth [4]. As cancer progresses further, cancer cells undergo a radical transformation from the epithelial phenotype to a mesenchymal-like (quasi-mesenchymal) phenotype and undergo metastasis by invading the lymphovascular system through intravasation and extravasation. Metastasis from the primary site to other organs and the lymphatic system limits the efficacy of cancer therapy and is the principal reason for increased rates of mortality [5].

## CONVENTIONAL STRATEGIES OF CANCER THERAPY: CURRENT STATUS AND LIMITATIONS

The various treatment strategies used in the clinical management of cancer have been depicted in Fig. (**1**). In case of localized tumors, surgical resection is performed. For example, in primary HCC cases, surgical resection and/or organ transplantation is advised by the clinicians. However, cases of tumor relapse or non-resectable tumors require other treatment modalities.

Radiation therapy (also called radiotherapy) is a therapeutic regimen that involves the use of high-energy X-rays or other particles to target and kill cancer cells and thereby, shrink tumors. Photodynamic therapy or phototherapy, on the other hand, uses a drug that is activated by light derived from laser or LED sources, to kill cancer cells in localized parts of the body. Both radiotherapy and phototherapy elicit drastic side effects. Some of the common side effects associated with radiotherapies include nausea, vomiting, skin irritation, ulceration, and loss of appetite [6]. In targeted therapies, specific receptors on the surface of cancer cells are precisely targeted. This approach ensures that normal cells remain unaffected

by the action of chemotherapeutic drugs and prevents tumor relapse to a certain extent. Hormone therapy is used for treating certain breast, prostate, and endometrial (uterine) cancers. This approach is used to slow the growth of cancer cells by inhibiting hormone production or preventing cancer cells from accessing the hormone. The immunotherapy approach aims at using drugs to boost or alter a person's immune system, which improves the susceptibility of cancer cells towards immune response [7]. The inhibitors of immune checkpoint molecules, such as CTLA-4 and PD-1, are currently undergoing clinical trials. Gene therapy incorporates the transfer of new genes into a cancerous cell or the adjacent tissues in order to either induce cell death or impede the growth of the cancer [8]. This treatment modality is relatively new, compared to the others, however, it is a very flexible regimen and a vast array of genes and vectors are currently being tested in clinical trials as of date.

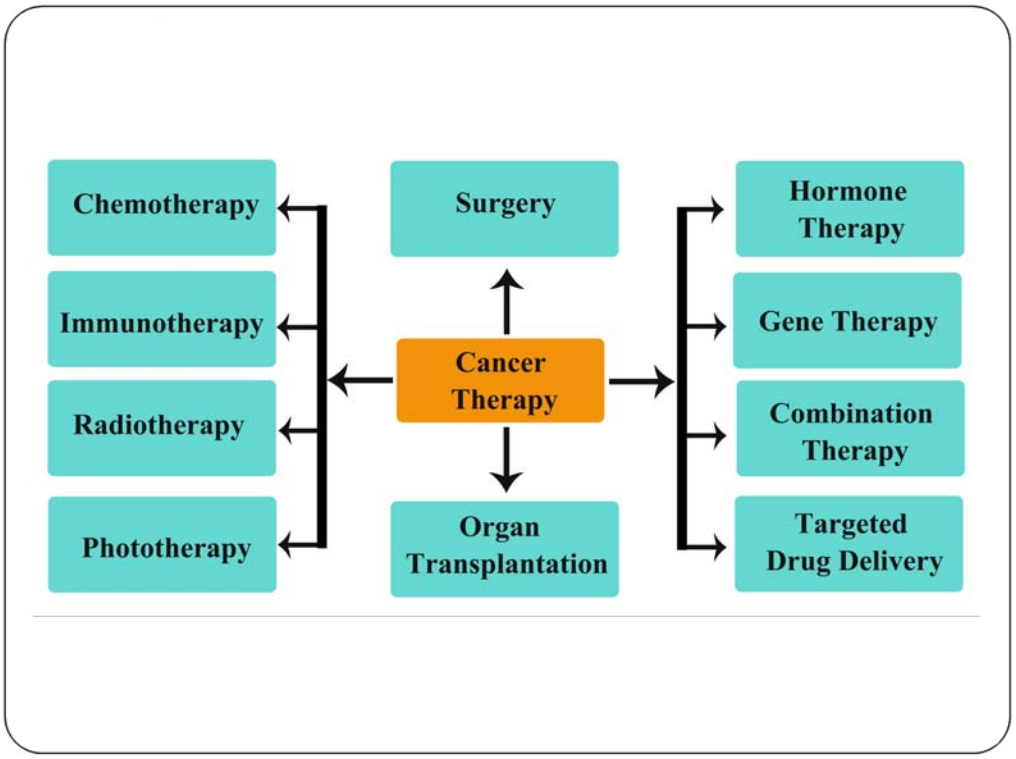


**Fig. (1).** Schematic representation of various therapeutic strategies used in the treatment of cancer.

Chemotherapy employs the use of powerful chemical substances to systemically destroy and kill cancer cells and is the most commonly used treatment modality against cancer. There are over 300 chemotherapeutic drugs that have been

# CHAPTER 5

# Antioxidant-Oxidative Stress Balance in Chemoprevention of Cancer

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**Abstract:** Every year, millions of individuals are diagnosed with cancer, making it one of the primary causes of mortality worldwide. It is estimated that around 10 million cancer-related deaths will occur, emphasizing the enormity of the impact of this disease on individuals and society as a whole. There are a multitude of side effects associated with anticancer drugs, and each drug, regardless of its class, has its unique set of adverse reactions. The overproduction of reactive oxygen species (ROS) and consequent accumulation of oxidative stress are significant contributors to adverse reactions, particularly for medications directed towards DNA. This issue has prompted the exploration of various dietary supplements to mitigate these unwanted side effects. Among these supplements, antioxidants have become increasingly prevalent as a chemotherapy adjuvant. Nevertheless, many cancer specialists discourage the consumption of antioxidant-rich supplements, as they have the potential to interfere with cancer-killing modalities that generate free radicals. There is ongoing debate regarding whether the use of antioxidant supplements impacts the effectiveness of cancer chemotherapy. Specific antioxidant supplements may lessen toxicities and bad effects, according to limited evidence that is both high quality and sample size. In this chapter, details of the role of antioxidants in cancer therapy and chemoprevention are discussed.

**Keywords:** Antioxidant, NKD2, Oxidative stress, Pro-oxidants, Reactive oxygen species.

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# INTRODUCTION

## Cancer and Oxidative Stress

Millions of individuals are diagnosed with cancer each year, making it one of the top causes of mortality in the world. According to estimates, there will be roughly 10 million cancer-related fatalities (9.9 million excluding non-melanoma skin cancer) and 19.3 million newly diagnosed cases of cancer worldwide in 2020 [1, 2]. This highlights the importance of continued research, prevention, and early detection efforts to help combat this global threat and improve outcomes for those affected by cancer.

Oxidative stress is a biological process that occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the ability of the body to neutralize and repair their damaging effects [3]. ROS are highly reactive molecules that are naturally produced in small amounts during normal cellular metabolism [4]. However, when their production exceeds the body's capacity to detoxify them, they can cause damage to cellular structures such as lipids, proteins, and DNA, leading to oxidative stress [5]. Cancer is a complex disease characterized by uncontrolled growth and spread of abnormal cells. It is the leading cause of death worldwide and has been extensively studied to understand its underlying causes, including the role of oxidative stress. Emerging evidence suggests that oxidative stress plays a significant role in the development and progression of cancer [6].

### *Sources of Oxidative Stress in the Body*

ROS are natural by-products of various metabolic processes in the body, but they can also be generated in excess due to certain external factors. Here are some sources of oxidative stress in the body:

1. Metabolism: One of the primary sources of ROS in the body is the process of cellular metabolism. During normal cellular respiration, which occurs in the mitochondria, ROS are produced as by-products of the energy production process. These include superoxide anion (O2-), hydrogen peroxide (H2O2), and hydroxyl radical (OH-) [7]. While ROS play a role in various physiological processes, excessive production or accumulation of ROS can lead to oxidative stress [8].

2. Environmental factors: Exposure to environmental pollutants and toxins can also trigger oxidative stress. For example, air pollution, including particulate matter, vehicular emissions, and industrial pollutants, can generate ROS in the body when inhaled, leading to oxidative stress [9]. Similarly, exposure to heavy

metals such as lead, mercury, and cadmium can also generate ROS and cause oxidative stress [10 - 12].

3. Unhealthy diet: A diet high in processed foods, fried foods, trans fats, and sugar can contribute to oxidative stress [13, 14]. These foods can increase the inflammation in the body [15] and decrease the activity of antioxidant enzymes, leading to an imbalance between ROS production and neutralization.

4. Lifestyle factors: Certain lifestyle choices such as smoking [16], excessive alcohol consumption [17], and lack of physical exercise can contribute to oxidative stress [18]. According to research conducted on animals, inactivity boosts the expression and activity of vascular NADPH oxidase and increases the generation of vascular ROS [19].

5. Inflammation: Chronic inflammation in the body can generate ROS as immune cells produce them as part of the immune response. Likewise, in cases of persistent inflammatory disorders, it is plausible that ROS (reactive oxygen species) derived from myeloid cells may trigger oncogenic mutations, providing a rationale for the heightened susceptibility to cancer observed in individuals with conditions such as Crohn's disease and inflammatory bowel disease [20]. A significant contributing factor to age-related illnesses and cancer is chronic inflammation and oxidative stress [21].

6. Radiation exposure: Exposure to ionizing radiation from various sources such as medical imaging (X-rays, CT scans) [22], and UV radiation from the sun can also generate ROS and DNA damage [23, 24].

7. Aging: Aging is associated with an increased risk of oxidative stress as the body's natural antioxidant defense mechanisms may decline with age [25]. This can result in an accumulation of ROS and increased oxidative damage to cells and tissues.

### *Effects of Oxidative Damage at Cellular Level*

One of the key mechanisms by which oxidative stress contributes to cancer is through DNA damage. ROS can directly interact with DNA, causing modifications to its structure and function. The hydroxyl radical directly damages DNA by oxidising the pyrimidine and purine [26]. This DNA damage can lead to mutations [27], which can disrupt the normal control mechanisms of cell growth and division, and ultimately result in the formation of cancer cells [28]. Additionally, ROS can also induce inflammation and promote the release of pro-inflammatory molecules, which can further contribute to DNA damage and cancer development [29].

# CHAPTER 6

# Inhibition of Nitric Oxide and Free Radical Production by Leaf and Stem Extracts of *Psychotria nilgiriensis*

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**Abstract:** *Psychotria nilgiriensis* was used in traditional medicine as to cure chronic inflammatory diseases. Therefore, the evaluation of different combination of solvent-based fractions from stem and leaves of *P. nilgiriensis* for free radical scavenging activity, inhibitory potential against nitric oxide radicals, and tentative identification of active metabolites were carried out. The antioxidant activity of solvent extracts was determined by $DPPH^{\cdot}$ scavenging, TAC, and ORAC assays using spectrophotometer analysis. Further, nitric oxide production inhibition was studied in lipopolysaccharide (LPS)-activated macrophages RAW 264.7 cells. Fraction-based bioactive chemical compound identification was performed using an LC-MS metabolomics approach. With each of the assays, activity was observed with various extracts derived from both the stem and the leaf. The two active extracts, one obtained with *Psychotria nilgiriensis* leaf ethyl acetate: methanol (PLEM, 40/60 v/v), and another one obtained with *P. nilgiriensis* stem chloroform: ethyl acetate (PSCE, 70/30 v/v), about 10-15% of the chemical components were identified. With PLEM, N,N-bis(2-ethylhexyl)hydroxylamine was higher in concentration, whereas PSCE, N,N-dioctylhydroxylamine was higher in concentration compared to other metabolites. Thus, the present findings suggest that the *P. nilgiriensis* leaf and stem could have medicinal value as an antioxidant for the treatment of inflammatory diseases. Some of the chemical constituents such as hydroxylamine derivatives could also be of value.

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**Blassan George (Ed.)**

**Keywords:** Antioxidants, Inflammation, Nitric oxide, *Psychotria nilgiriensis*, Polyphenolics.

## INTRODUCTION

Free radicals may be generated during the biochemical process and balanced by antioxidant enzymes present in the human body. However, excessive production of free radicals can lead to oxidative stress and develop chronic inflammatory degenerative diseases [1]. The development of inflammation is induced by oxygen radicals including nitric oxide (NO) which are produced by nitric oxide synthase. This pathophysiological process are also mediated by leukocytes, macrophages, mast cells, and platelets, *etc*. Thus excessive number promotes tissue injury and neurodegenerative disease [2]. Research studies reported that prostaglandin-biosynthesis has significantly contributed to the development of the cardinal signs of inflammation [3]. The prostaglandins are lipid autacoids that was derived from the arachidonic acid pathway. Prostacyclin, prostaglandin F2, prostaglandin D2, and prostaglandin E2 are the four principal bioactive prostaglandins that are involved in the patho-physiological process leading to the cause of the classic signs of inflammation [3]. Moreover, COX enzymes such as COX-1 and COX-2 are the two isoforms responsible for the synthesis of prostaglandins. The COX-1 is constitutively expressed and involved in maintaining cellular homeostasis. Whereas, COX-2 is readily expressed in the LPS, mitogens, reactive oxygen intermediates, and inflammatory cytokines in gastrointestinal epithelial cells [4]. Thus, free radicals like NO stimulate inflammatory mediators and cause many degenerative diseases. Therefore, potential free radical inhibitors or anti-inflammatory agents are needed to prevent oxidative stress related disorders. The non-steroidal inflammatory drugs (NSAIDs) effectively inhibit prostaglandin synthesis, but untoward side-effects are common [5]. Therefore, it is of interest to search for safe and effective antioxidant and anti-inflammatory agents to inhibit prostaglandin production. Herbal medicines prepared from plant leaves, bark, or stem is used for treating illnesses and side-effects are reportedly negligible. Although definitive clinical trials showing the value of herbal medicines in the treatment and prevention of diseases are rare, the use is becoming more mainstream as improvements in the analysis and quality control continue.

The genus *Psychotria* belongs to the family of Rubiaceae, which contains indole alkaloids such as brachycerine and psychotridine known to be, medicinally important compounds to mediate biological responses against analgesia. The tender stem of *Psychotria* has potential the treatment of rheumatism when eaten with honey. This traditional remedy is used by, the Irula tribes of Thottabeta in the Nilgiris district [6], and the Kanikkar tribes of Kalakad, Mundanthurai in the Tirunelveli district, Tamilnadu, India [7]. *P. nilgiriensis* has been used for medi-

cinal purposes and the polyphenolic content of this plant extracts showed good antioxidant, antimicrobial [6], analgesic, and anti-inflammatory activities [8]. It is therefore evident that *P. nilgiriensis* may have the potential to exhibit anti-inflammatory activity. However, individual phytoconstituents responsible for antioxidant and anti-inflammatory activity has not been reported in the stem and leaf of *P. nilgiriensis*. Thus, in the present study, *P. nilgiriensis* stem and leaf fractions were evaluated against free radicals and NO production using RAW 264.7 cells treated with lipopolysaccharide (LPS). In addition, the present study also attempted to identify some of the active components in the stem and leaf extracts using LC-MS.

## MATERIALS AND METHODS

### Chemicals

All the chemicals (analytical grade) were purchased from Sigma-Aldrich (Carlsbad, California, USA).

### Collection and Identification of Plant Materials

The fresh parts of the stem and leaves of *P. nilgiriensis* were collected during the month of September 2012 from the Nilgiris, Tamil Nadu, India. The plant was taxonomically identified and confirmed and a voucher specimen was deposited in the Botanical Survey of India, Coimbatore, Tamil Nadu, India. The collected plant materials were washed with water to remove surface pollutants and the stem and leaf parts were air-dried in the shade for ~ 5 days.

### Preparation of Crude Extracts using Solvents from Plant Materials

The dried samples (100 g) of leaf and stem were powdered using the mechanical grinder packed in a Whatman No. 1 filter paper and extracted with Soxhlet apparatus using methanol (400 mL) at 40 °C for 48 hrs. The solvent concentration of the various solvent extracts of PL and PS were concentrated by rotary vacuum evaporator (RE300; Yamato Scientific America Inc., Santa Clara, CA, USA). Next, the methanol extract of *P. nilgiriensis* leaf (PL) and stem (PS) were again re-extracted successively with Soxhlet apparatus using the different solvent ratio for 48 hrs presented in Table **1**.

For purity, each time before extracting with the next solvent, the plant powder was air-dried at room temperature. Again, the solvent concentration from the various extracts of PL and PS were concentrated by using a rotary vacuum evaporator. Then, the extracts were dissolved in respective organic solvents at 1 mg/mL concentration and used for further assessment.

CHAPTER 7

# Plant-Derived Compounds for Chemoprevention and Chemotherapy: From Molecular Mechanisms to Clinical Trials

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**Abstract:** Cancer is still a disease that many people fear. Cancer patients frequently have side effects from chemo- and radiotherapy that lower their quality of life and may force them to stop receiving their treatment. For centuries, people have employed natural products, particularly plants, to heal a wide range of illnesses. Powerful bioactive compounds that are produced from plants can be employed as medications. The uniqueness and potency of anticancer therapeutic medicines originating from plants are now being explored in research studies. Using sophisticated analytical techniques, the healthcare industry is attempting to comprehend the physio-chemical characteristics of these plant derived compounds and their contributions to the treatment of cancer. Some of these compounds are thought to be candidates for use as chemopreventive medicines and may even be combined with traditional chemotherapy in certain circumstances. The purpose of this book chapter is to highlight important plant derived compounds, their properties, mechanism of action and ongoing clinical trials for cancer prevention and treatment. The suitability and lethality of medicinal and herbal plants are a subject of considerable debate despite their many powerful benefits. Here, we discuss advantages, limitations and current status of recruiting plant derived compounds as chemopreventive and chemotherapeutic drugs.

**Keywords:** 3,3'-diindolylmethane, Anthocyanin, Anticancer, Beta-carotene, Cancer treatment, Cancer, Chemoprevention, Chemotherapy, Clinical studies, Drug discovery, Plant derived compounds.

## INTRODUCTION

The GLOBOCAN 2020 estimated that over 19.3 million individuals worldwide received a cancer diagnosis in the year 2020, and approximately 10 million people

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died from the disease [1]. In both developed and developing nations, cancer poses a serious threat to public health. Surgery, radiotherapy, and chemotherapy are the three major treatments (therapies) used to treat or cure cancer. For at least half of all cancer patients, radiation therapy continues to be a crucial part of their overall care, despite the negative effects it has produced. Similarly, chemotherapy always results in harm to the healthy tissues surrounding the tumor.

One of the primary negative consequences brought about by radiation therapy in cancer patients is chromosomal abnormalities. In cancer patients who have received radiation therapy, structural chromosomal abnormalities and numerical or copy number variations are seen. According to recent research, radiation therapy-induced mutations in cellular DNA can be passed on and can be manifested in the surviving cells' progeny. Therefore, radiotherapy could be a possible risk factor for subsequent malignancies, whether it is combined with chemotherapy or not [2]. Cancers that develop even after the main malignancy has received initial therapy are referred to as subsequent malignancies.

Chemotherapeutic drugs target cells, both tumor cells and non-tumor rapidly proliferating cells that have a high basal level of proliferation and regeneration. This is what contributes to the high amount of toxicity that these therapies have [3 - 5]. The gastrointestinal tract cells, bone marrow cells, and hair follicle cells - all of which proliferate quickly under normal circumstances are all destroyed by chemotherapy. Mucositis, alopecia, and decreased production of blood cells are most often reported side effects during the course of chemotherapy treatment [6]. Chemotherapy is connected to a wide variety of symptoms and unfavorable side effects that can be modest to severe and incapacitating. For patients starting cancer chemotherapy, nausea and vomiting are two of the most anticipated side effects. In addition to this, chemotherapy for cancer patients frequently causes severe gastrointestinal side effects that can be both uncomfortable and dangerous. Thus, minimizing physical and psychological therapy side effects requires early identification and appropriate care of these symptoms by physicians and patients.

Chemoprevention is a method of preventing the development of cancer by using substances, such as medications and dietary supplements that may target certain pathways that contribute to the propagation of cancer. Chemopreventive medications are mostly utilized in cancer patients who have premalignant lesions or who are at high risk of getting the disease. To be safely provided to high risk, cancer-free people, a cancer chemopreventive drug must not be toxic to normal tissues. A chemopreventive drug should, ideally, have specific targets that are highly expressed in malignant or premalignant lesions but not in healthy tissues. As cancer chemopreventive agents, various natural and artificial substances have been tested so far [7, 8].

Since ancient times, people have understood the value of using natural materials as a source for treatments. Drugs produced from natural products continue to significantly contribute to drug discovery today despite significant scientific and technological advancements in combinatorial chemistry. A huge chemical varieties are found in the millions of species of plants, animals, marine creatures, and microbes, making nature an appealing source of novel therapeutic candidate chemicals [9]. Due to their diverse structural makeup and favorable pharmacological and molecular properties, natural compounds and their derivatives have shown tremendous potential for the development of chemotherapeutics. Natural bioactive substances and conventional chemotherapeutic medications can be combined to increase anti-cancer effectiveness and lessen adverse effects. It has been demonstrated that natural products, including raw extracts, fractions rich in bioactive substances, pure chemicals obtained from herbs, and herbal formulations, can both prevent and treat cancer. The chemo- or radio-resistance of cancer cells may occasionally be overcome by the addition of bioactive substances [10]. There is evidence from clinical trials and preclinical studies that certain natural products can lessen the gastrointestinal toxicity, hepatotoxicity, hematological system damage, cardiotoxicity, neurotoxicity, and nephrotoxicity brought on by chemotherapy and radiation [11, 12].

In this book chapter, we aim to provide an updated overview of the chemical composition, mechanism of action, *in vitro* research, and ongoing clinical trials of a number of important anti-cancer natural products. These natural products are known to enhance treatment precision, lower recurrence, and enhance patients' quality of life. Depending on the kind, stage, and body area affected by cancer, a wide variety of natural products are available to combat this disease.

## SIGNIFICANCE OF NATURAL COMPOUNDS FOR CANCER THERAPY AND CHEMOPREVENTION

Significant efforts have been undertaken over the past few decades to separate unique natural compounds from bacteria, plants, and other living things in order to evaluate their anticancer characteristics and learn more about their mode of action. A panel of anti-cancer medications had been discovered as a result of these attempts. There have been several reports of compounds having anticancer properties or special structural benefits in therapeutic target methods [13]. Ancient medical writings mention surgery but also prescribe some natural, primarily plant-based products. This provides an intriguing point of comparison with modern medical understanding. The development of anticancer natural compounds has been significantly influenced by large-scale anticancer drug discovery and screening initiatives, such as those supported by the National Cancer Institute. Natural product-based drug discovery has grown during the past

CHAPTER 8

# Medicinal Plants and Cancer Therapy and Chemoprevention

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**Abstract:** Cancer is still the second-leading cause of death in industrialized countries. The development of resistance to anticancer drugs and the severe side effects of current drugs prevent treatment with drug doses high enough for long-lasting remissions or sustainable cures. There have been unprecedented efforts to uncover new treatments and the knowledge of cancer has been tremendously increasing for the past few decades. Medicinal plants are a fertile ground to be used as phytotherapy and to isolate phytochemicals with interesting pharmacological features. Medicinal plants are being increasingly documented as useful consistent treatments for cancer. A large volume of clinical studies have reported the beneficial effects of herbal medicines on the survival, immune modulation, and quality of life (QOL) of cancer patients when these herbal medicines are used in combination with conventional therapeutics. This book chapter should provide useful technological support for the evidence-based application of herbal medicines in cancer therapy. Natural products have always been a major source of drug development in cancer therapy.

**Keywords:** Chemopreventive agents, Cancer therapy, Chemotherapy, Medicinal plants, Side effects.

## INTRODUCTION

Cancer is the dreadful and deadliest disease that can affect all organs of the body and elicits 18.1 million incidences, and 9.6 million fatalities today, and will cause 29.5 million new cases by the year 2040 as publicized by the International Agency for Research on Cancer (IARC). This fatal disease attacks one in 6

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women and one in 5 men during their life span globally. Out of 11 women and 8 men diagnosed with cancer, each one in both cases dies eventually from the disease. Despite surgical removal of tumors and various therapies such as radiation, chemotherapy, immunotherapy, hormone, stem cell, precision medicine, platinum, etc., are used to treat people with cancer.However, they are associated with few drawbacks and side effects [1].

With a large number of deaths reported, cancer still stands as a threatening disease.

Various attempts are being made worldwide to come up with an efficient anticancer drug with a high therapeutic index and target-specific tendency [2]. Mitigating efforts to vanquish the drawbacks triggered the exploration of more potent medicines such as bioactive components from medicinal plants. Plants are reservoirs for novel chemical entities and provide a promising line for research on cancer. In many countries, herbal medicines have been used as the primary source of medical treatment due to their natural antiseptic properties and they play a vital role in the healthcare system of a large number of countries [3, 4].

Medicinal plants act as an important anticancer drug, containing bioactive compounds that are responsible for their pharmacological actions in the human body. Herbal drugs (*e.g.*, polyphenols, brassinosteroids, and taxol) are desired for anticancer treatment, due to their easy availability, being less expensive and having lower side effects [5]. In many countries, plant extracts are widely used as important sources of chemotherapeutic agents than synthetic drugs and over 60% of anticancer agents are derived from natural resources [6], including plants, marine organisms, and microorganisms. The anticancer activity of herbal plants for various types of cancers has been examined by clinical studies and phytochemical screening. They possess immunomodulatory and antioxidant properties, leading to anticancer activities as they have versatile immunomodulatory activities by stimulating both non-specific and specific immunity [7].

Chemoprevention is a novel approach to control cancer. Cancer chemoprevention involves the use of natural or synthetic chemicals to delay the reverse carcinogenesis. Accurate dosage is a vital factor in cancer prevention and treatment. In the last few decades, phytoconstituents derived from the medicinal plants have been extensively studied for cancer chemoprevention using preclinical models. Consumption of chemopreventive agents containing phytocompounds shows an important insight to fight against cancer and yield promising outcomes. Products from natural sources such as medicinal plants and herbs show protective effects against various forms of cancers. The preclinical evidence for cancer

chemoprevention by some phytochemicals isolated from medicinal plants is quite persuasive.

A number of anticancer compounds including Taxol, vincristine, vinblastine, camptothecin derivatives, irinotecan, topotecan, and etoposide obtained from epipodophyllotoxin are in experimental mode worldwide. A few potential agents like roscovitine, flavopiridol, betulinic acid, combretastatin A-4, and silvestrol are in the developmental phase in laboratories [8]. Some of the anticancer agents for example isothiocyanates from cruciferous vegetables and withaferin A (WA) derived from a *Withania somnifera* already entered clinical investigations, which have an interesting feature of the structurally diverse phytochemicals. They target mitochondria to provoke cancer cell-selective death programs. Recent studies have indicated that mechanisms involved in the chemopreventive action may include combinations of anti-oxidant, anti-inflammatory, immune enhancing, and anti-hormone effects. Further, the modification of drug-metabolizing enzymes influences on cell cycling and differentiation, induction of apoptosis, suppression of proliferation and angiogenesis, which play a role in the initiation and secondary modification of neoplastic development which is under investigation.

In this regard, the aim of this chapter is to highlightvarious types of medicinal plants and their utilization as chemopreventive agents for the treatment of cancer.

## Medicinal Plants

Plants are an effective source of anticancer agents. Medicinal plants play a key role not only as traditional medicines but also as trade commodities. Nowadays, there is an increased interest in herbal-based medicines due to the increasing realization of the potential health hazards associated with the indiscriminate use of modern chemically-derived medicines. Medicinal plants play an important role in revealing novel anticancer drug molecules, in which bioactive compounds are more tolerated and nontoxic to normal human cells. In fact, there are several medicinal plants all over the world, including in India, that are being used traditionally for the prevention and treatment of cancer [9, 10].

Research is being carried out throughout the world to find out a suitable chemo-protective agent. Nature has always been a great contributor towards this goal. After the isolation of vinca alkaloids such as vinblastine and vincristine, a new era in the use of plant material as anticancer agents started [11]. They were the first anticancer agents in clinical use for the treatment of cancer. Plant-derived natural products such as terpenoids, flavonoids, and steroids have received considerable attention due to their diverse pharmacological properties, which include cytotoxic and chemopreventive effects. Several studies have been performed on medicinal plants to know about their cytotoxic nature. From the

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