ALTERNATIVE REMEDIES AND NATURAL PRODUCTS FOR CANCER THERAPY:

AN INTEGRATIVE APPROACH

Editors:
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Alternative Remedies and Natural Products for Cancer Therapy: An Integrative Approach

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FOREWORD

Cancer is the second leading cause of mortality worldwide. Integrative therapies and botanicals are sought for their ability to exhibit anti-carcinogenic activity *via* interfering with the onset and progression of cancer at various stages such as cellular proliferation, differentiation, apoptosis, angiogenesis, and metastasis. Nature offers a vast untapped repository of biomolecules possessing structural diversity that could be mined for their potential application in cancer therapy. Integrative medicine is now acknowledged worldwide, and efforts are going on to understand these systems through the lenses of modern science. The authors of the book "Alternative Remedies and Natural products for Cancer: An Integrative Approach" have brought an excellent compilation of recent findings in this domain and present an elaborate discussion on the mechanisms, efficacy, and utility of complementary systems approach to alleviation, mitigation and techniques for addressing varied types of cancers. Through this book, the authors emphasize, educate and appreciate the importance of the translational role of botanical and integrative approaches such as acupuncture, yoga, alternative therapies, the role of phytochemicals, dietary supplements, *etc*. This book provides a holistic view of all the translational approaches and botanicals used in cancer treatment and acquaints us with modern techniques in anticancer drug discovery from a botanical perspective which will be very useful especially to researchers, medical practioners, P.G. students, PhD scholars and society including the common man in order to understand the reality of translational approaches in addressing cancer, its treatment and prevention

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PREFACE

The purpose of the book is to understand, emphasize, and appreciate the role of complementary and alternative medicine systems like Ayurveda, Acupuncture, Yoga, Mudras, Aromatherapy, and Homeopathy in the management of cancer. One of the vital factors that affect the development and spread of this disease is the lack of immunity and resistance. Through this book, we intend to offer our readers an amalgamation of interesting topics like natural immune-boosting foods, recipes, and herbs that fight against cancer coupled with modern drug discovery techniques such as in silico methods, High-throughput screening, and methods to convert these herbs into leads with suitable illustrations. This book emphasizes the role of spirulina, super green foods, weeds, African herbs, mushrooms, multi-targeting anticancer phytochemicals, and terpenoids as modern anticancer botanicals in the 21st century and botanicals acting on important targets like human topoisomerases I & II, and caspases in addressing cancer through translational approaches. The contents of the proposed books cater to a diverse audience from domains of food and nutrition, pharmaceuticals, medicine, and practitioners of CAMS and help them in understanding the ethnopharmacological, nutraceutical, phytochemical, and systems approach to cancer therapy.

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CHAPTER 1

Clinical Role of Modern Ayurveda in Treating Cancer

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Abstract: "Ayurveda", an ancient Indian science of living which originated about 5000 thousand years ago, establishes ways of living a healthy life by establishing harmony between body, mind, and spirit. Ayurveda suggests lifestyle and dietary changes for the management of cancer and cancer like symptoms. Though the occurrence of this disease about five thousand years ago was sparce, yet the ayurvedic texts do mention some symptoms that can be aliased to cancer. These are often treated by different Ayurvedic procedures and formulations. Majority of these formulations balance the elements in our body referred to as "*Tridoshas*" which are *vatta, pitta* and *kapha*. It has been reported that the herbs, lifestyle and dietary changes that act by balancing "*Tridoshas*" show beneficial effects on cancer at various stages of the disease. Medicinal plants that possess a set of defined attributes such as bitter, pungent, astringent biopotency, act as excellent candidates for prevention, mitigation and treatment of cancers. Moreover, using systems pharmacology and bioactivity-guided fractionation, it is now possible to decipher the molecular mechanism of action of these potent anti-cancer herbs. An amalgamation of Ayurvedic systems and modern medicine put together as "Modern Ayurveda" is proving efficient in cancer therapy.

Keywords: Ayurveda ayush, Cancer treatment, *Grandhi* and *Arbuda*, Herbs, Neoplasm, Tridosha.

INTRODUCTION

Ayurveda meaning "Science of Life" is an ancient Indian system of medicine which dates to more than 5000 years ago. Ayurveda focuses on the holistic healing *viz*. well-being of body, mind and soul for elimination of disease conditions. Ayurveda is still practiced worldwide in the 21st century with more

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than 7 lakh practitioners currently registered in India itself. The ayurvedic practitioners called *vaidyas*, use patient-centric method of treatment, after a personalized diagnosis [1, 2]. This system is well documented in the ancient scripts and focusses on curing the root cause of diseases rather than being a mere symptomatic treatment.

The interest in traditional medicine has recently resurged owing to an increase in incidences of chronic diseases, cases of antibiotic resistance amongst micro-organisms, multi-drug resistant cancers and the emergence of newer disease conditions such as COVID-19. Ayurvedic therapies have been proven beneficial in the management of various disease conditions which are thought to be incurable by allopathic system of medicine, *e.g.*, diabetes, arthritis, and most importantly cancer [3 - 5].

Ayurveda describes the health condition of individual as a combination of *Tridoshas* (body humor) *viz vata* (air), *pita* (fire) and *kapha* (water) based on motion, digestion and cumulation, which remain constant throughout one's life [6]. The imbalance or inequilibrium of these doshas is referred to as "*vikruti*" and leads a disease condition [7]. The physical or mental condition of an individual can cause this imbalance, eventually affecting the body.

Ayurveda uses varied approaches which aid in the mitigation and treatment of disease conditions. These include massage, meditation, yoga, diet, medicine and surgery. It also uses techniques such as panchakarma for detoxification of body [8, 9]. The ayurvedic practitioners prescribe consumption of certain drugs to cure a person of disease conditions. Many Ayurvedic medicines, referred to as "*rasayanas*" are based on herbal products. Medicinal plants (*dravyas*) have been consumed traditionally for their healing properties. The usage and preparations of medicinal plants have also been listed in Ayurvedic scriptures. These Ayurvedic drugs include some of the most commonly found flora in the Asian subcontinent [10]. Ayurvedic drugs are formulated into different dosage forms for enhancing their palatability, potency, and shelf-life. Ayurvedic scriptures mention various formulations such as *arka, taila, ghrita, vati, asava, arista, lepa etc*. to obtain the best properties of single herb, polyherbal or herbo-mineral preparations [11].

CANCER: AYURVEDIC PERSPECTIVE

The incidences of disease conditions such as cancer in the time of development of Traditional Medicinal systems were minimal, as a result, very few texts describe this condition. With the onset of the 21st century, the incidences of cancer are on the rise owing to changes in diet, lifestyle, stress, environment, *etc*. The vital books of Ayurvedic medicine *viz*., *Charaka Samhita* and *Sushruta Samahita* describe methods of cancer detection, mitigation, management, and cure [7].

Pathophysiology of Cancer as per Ayurveda

Cancer is a condition manifested when cells in the human body undergo uncontrolled division and inflammation. The different factors that lead to precipitation or build-up of tumours in the body have been postulated in ancient texts. Mostly abnormal interactions between *prakriti* (genotype) and environmental factors vitiate the *doshas* (body humour) and impair immunity, which can lead to aberrant cell growth and sometimes cancer. Table **1** summarizes the effect of different food and other factors on *doshas*. Moreover, the interaction between vitiated *doshas* (body humour) and weak *dhatus* (body tissues) manifests as cancers of a specific organ [12].

Table 1. Types of doshas and their corresponding aggravating factors [12]

Dosha (Body Humor) Involved	Aggravating Factors
Vata	Excessive consumption of bitter, pungent, astringent, dry foodstuff and stress.
Pitta	Excessive consumption of sour, salty, fried food and excessive anger.
Kapha	Excessive consumption of sweet, oily food and sedentary lifestyle.

Another theory about the cause of cancers in a body, obtained from the traditional texts, as described by Rao (1994) states that cancers can arise out of metabolic imbalances in body, involving proteins and enzymes. The body fire (*dhatwagni*) regulates the metabolic processes in the body. This body fire can be classified into four categories: low (*mand*), medium (*sama*), high (*tikshna*) and nil (*vishama*) depending upon intensity and is responsible for all enzymatic processes in the body. When the body fire decreases to nil condition (*vishama*), the cell losses its characteristic pattern of protein synthesis, leading to the production of altered proteins and metabolism of amphibolic substances. The presence of these substances is characteristic of a tumour cell [13].

An additional theory from *Sushruta Samhita* states that the consumption of Kapha aggravating substances decreases the intensity of body fire which in turn slows down the digestive and metabolic processes resulting in the formation and accumulation of toxins (*ama*) in our body. The toxins then interact with different body tissues (*dhatus*) and alter its functioning, slowly leading to systemic blockade and stagnation thus initiating various pathological processes [14]. When this overrides the limit, there is a diversion of flow in these channels and alteration in the functions of body tissues. This leads to the formation of neoplasms into various organs and tissues. The decrease in the body fire, is inversely proportional to the related tissue size. Consequently, the tissue size increases resulting from cell proliferation and tissue growth. If these events

CHAPTER 2

Aromatherapy: An Adjuvant Treatment in Cancer

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Abstract: Aromatherapy is a complementary healing therapy that uses aromatic essential oils to improve the health of the body and mind. Essential oils with healing properties, like geranium oil, rosemary oil, lavender oil, patchouli oil, and others, have been used to treat cancer. Cancer is often treated using chemotherapy and/or radiation therapy. Nausea and vomiting are often side effects of chemotherapy and radiotherapy. Subsequently, these cancer therapies lead to various psychological disorders, such as stress, anxiety, and depression, in cancer patients. Hence, the a need to assist cancer patients in overcoming these disorders. Aromatherapy, which is a blend of essential oils, has been reported to improve disorders that arise during complicated cancer therapies such as chemotherapy and radiation. Research on cancer populations has revealed that patients exposed to essential oils *via* inhaler devices had reduced anxiety, stress, nausea, and poor sleep. The effects of aromatherapy are reported to be due to the binding of chemical components in the essential oil to receptors in the olfactory bulb, impacting the brain's emotional center, the limbic system. Aromatherapy has also been reported to relieve pain, muscular tension, and fatigue. Aromatherapy practitioners treat specific conditions using various combinations of oils and different modes of application. Aromatherapy can thus be used as a potential supplement treatment to improve complications in cancer; however, further studies are needed to estimate the protocol and standard dosage. Given the difficulties of cancer treatment, aromatherapy can play an important role in treating patients' psychological aspects.

Keywords: Aromatherapy, Aromatherapy practitioners, Brain's emotional center, Cancer therapies, Cancer, Chemotherapy, Essential oil, Geranium oil, Lavender oil, Psychological aspects, Patchouli oil, Radiation, Rosemary oil.

INTRODUCTION

Cancer is one of the greatest health challenges in the world. GLOBOCAN 2020 estimated about 19.3 million new cancer cases and 10.0 million cancer deaths in 2020 [1]. Although various advanced treatment and therapies are available, patients suffer from various complications such as such as loss of appetite, malnutrition, loss of hair, vomiting, dryness of mouth, fatigue, nausea, pain, wea-

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kness, and psychological disorders like anxiety, depression and stress [2]. Thus, the need arises for developing complementary and alternative methods which are not only effective in relieving cancer complications, but also having less side-effects. Alternative therapies have been commonly used in reducing the discomfort of the patients with cancer [3].

Aromatherapy has varied applications as complementary treatment in different diseases [4, 5]. This treatment is considered to be one of the natural ways of healing person's mind, body and soul. Aromatherapy comprises of the use of essential oils extracted from natural resources such as plants to treat various disorders [6]. Essential oils are known to be highly concentrated extracts with characteristic odor.

Literature survey reveals that aromatherapy can be used to improve complications arising in cancer patients such as fatigue, nausea, vomiting, loss of appetite, psychological disorders, *etc* [7 - 10].

Classification of Aromatherapy

Aromatherapy can be applied or administered in three ways, namely [11]: Medical aromatherapy is where essential oils are administered internally *via* oral, rectal, or vaginal routes. Only steam-distilled and expeller-pressed essential oils are used internally. Subtle aromatherapy is the inhalation of essential oils for psychological treatment. It is also called aromacology. In this therapy, essential oils are absorbed through the nasal membrane, which reaches the olfactory nerves and stimulates impulses. This impulse travels to the limbic system of the brain, where it has a relaxing and psychological effect [12]. Traditional aromatherapy uses essential oils applied topically by massage. It can be used in two forms: for therapeutic use or for cosmetic use. Therapeutically, essential oils can have physical as well as psychological effects.

Essential Oil Aromatherapy mainly comprises the controlled use of essential oils obtained from plants and administering them internally or externally based on individual needs to promote good health or treat any disorder. Essential oils are volatile oils extracted from various parts of aromatic plants. Essential oils are stored in secretory parts of the plant such as oil cells, resin sacs, epidermis, trichomes, *etc.* Essential oils are extracted from plants using various processes such as steam distillation, expression, enfleurage, solvent extraction, maceration, and supercritical fluid extraction [11]. Essential oils chemically consist of monoterpenes, aldehydes, ketones, esters, alcohols, *etc* [13]. They are volatile in nature and have a characteristic odour. Every individual plant produces varied types of essential oil that differ in chemical composition [14]. Due to variations in chemical composition, clinical effects can be distinctly different.

Essential Oil Chemical Composition

On the basis of the chemical structure, essential oils are broadly categorized into oxygenated compounds and hydrocarbon compounds [15]. Oxygenated compounds comprise esters, alcohols, phenols, aldehydes, ketones, oxides, *etc.* Hydrocarbons consist of mainly terpenes which have the basic isoprene (C_5) unit. Terpenes are further classified as monoterpenes (C_{10}), sesqueterpene (C_{15}), and diterpene (C_{20}). Terpenes can also be acyclic, monocyclic, or bicyclic.

Plants are used in Aromatherapy. Some well-known essential oils occur in Thymus vulgaris, Rosmarinus officinalis, Ocimum, Salvia officinalis, Lavender, Chamomile, and Melissa officinalis [11]. The most commonly used essential oils or aromas in cancer treatment are lavender, peppermint, orange, and chamomile [11]. Lavender is known to improve sleep quality and relieve psychological disorders. Peppermint is reported to be used for nausea and vomiting. Orange finds application in reducing anxiety, depression, *etc* [11]. Some of the essential oils derived from plants that can be used in aromatherapy for cancer patients are listed in Table **1**. Essential oils are typically dispersed in carriers, which are obtained by cold pressing or fixing vegetable oils such as sweet almond, grape seed, and so on. Many fixed vegetable oils such as calendula (Calendula officinalis) and St. John's wort (Hypericum perforatum) are known for their therapeutic activity. Other carriers include honey, Aloe vera and specially formulated gel and wax.

Table 1. Essential oil from plants for aromatherapy in cancer patients

Essential oil	Constituent	Possible mechanism	Ref
Eucalyptus oil	major- 1,8- cineol	Reduces the production of inflammatory cytokines that stimulate cancer cell growth.	[27]
Thymus fallax	Carvacrol, thymol	Cytotoxicity by anti-oxidant mechanism	[28]
Boswellia sacra	α-pinene, myrcene, boswellic acid	Antiproliferative	[29]
Lippia alba	Geranial, geraniol	Citral dependent cytotoxicity.	[30]
Zanthoxylum rhoifolum	β-caryophyllene, α-pinene, myrcene	Cytotoxicity.	[31]
Peppermint oil	Menthol	Reduces chemotherapy induced nausea and vomiting.	[32]
Cymbopogon flexuosus	Citral	Induces apoptosis.	[33]
Patchouli oil	α-guaiene, seychellene, α-patchoulene	Induces apoptosis and decreases cell growth.	[34]
Rosewood oil	Linalool	Cytotoxicity.	[35]

CHAPTER 3

The Traditional Immune Boosting Recipes

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Abstract: The immune system is amazingly complicated and vital for our survival. Several different systems and cell types of our body work effortlessly in ideal synchrony throughout the body to fight off pathogens and clear up dead cells. Our immune systems perform an implausible job by putting up a wall that can safeguard the disease-causing microorganisms. Our immune system requires equilibrium to function smoothly, so a person must eat and drink healthy balanced foods for getting energy and nutrients. The immunity related diseases may occur due to several factors such as seasonal change, environment factors, virus attacks, and simple stress. To combat these, we need to consume immunity-boosting foods and nutrients rich in antioxidants like *Alium sativum, Alium cepa, Citrus limon, Withania somnifera,Moringa oleifera*, *Curcuma longa*, *etc.*, which can build up the immunity. The traditional system of medicine like Ayurveda and Siddha system of medicine quoted several traditional immune-boosting recipes like Maha- sudharshnachoornam, Talisadichoornam, Dhanavantam, Gulika-churnam, sitophaladichoornam, *etc.* Several times it is proven that lifestyle and dietary changes can result in a better immune system. A healthy lifestyle includes consuming foods which help in boosting immunity. In addition to keeping a balanced diet in our daily life, there is a necessity for traditional immunity-boosting agents simultaneously. Traditional immunity-boosting agents are usually rich in vitamins, antioxidants, and other minerals and the requisite nutrients for maintaining equilibrium in the immune system. In this chapter, detailed information about Traditional immunity-boosting agents will be discussed.

Keywords: *Alium sativum*, *Alium cepa*, Antioxidants, *Citrus limon*, *Curcuma longa*, Disease-causing, Dhanavantam, Environment factors, Gulika-churnam, Healthy lifestyle, Immune system, Immunity, Immunity-boosting agents, Microorganisms, *Moringa oleifera*, Maha- sudharshnachoornam, Pathogens, Seasonal change, Safeguard, Simple stress, Sitophaladichoornam, Traditional, Talisadichoornam, Vitamins, Virus attacks, *Withania somnifera*.

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INTRODUCTION

***Immunity*:** Immunity can be defined as a very complex biological system which is endowed with the capacity to recognize and withstand anything that belongs to the body itself, and to distinguish and decline what is foreign. The immune system protects us from various invading pathogenic microorganisms and other immunosuppressive diseases like cancer. Immune system is a complex network of different specialized cells, tissues and chemical mediators (Fig. **1**) [1]. The immune system always plays a vital role in the defence system against any infection [2].

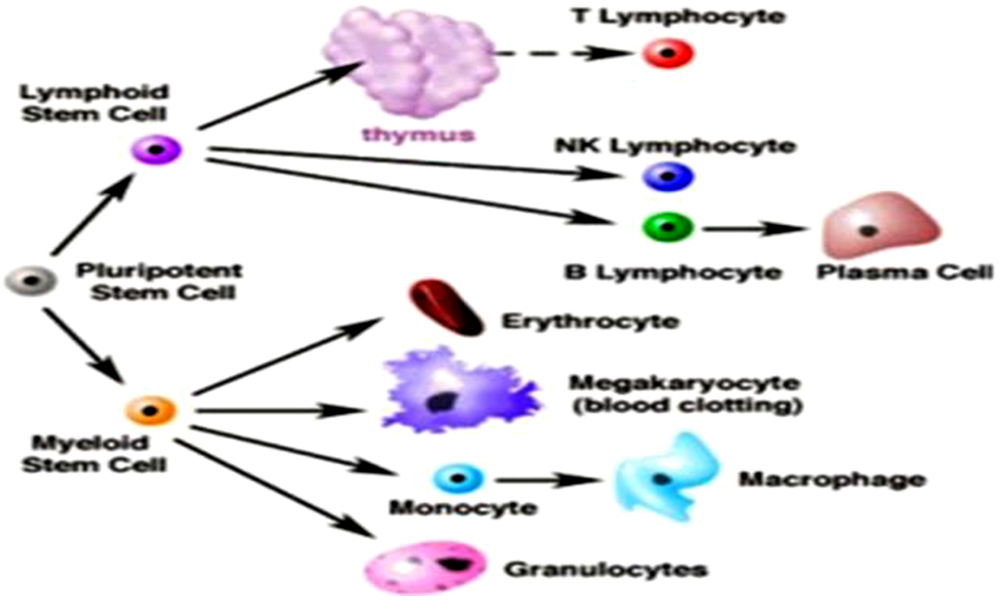

Fig. (1). Complex network of immune system [1].

Types of immunity: There are two types of immunity. Natural or innate immunity and adaptive immunity. All animals possess an ancient system of defence against the pathogens in which they are susceptible, which is called as innate, or natural, immunity and this includes two parts. The first part is called humoral innate immunity which involves a variety of substances found in the humors or body fluids. They interfere with the growth of pathogens or clump with them together to eliminate them from the body. The second part is called cellular innate immunity which is carried out by different cells called as phagocytes, which ingest as well as degrade pathogens. Innate immunity is nonspecific that is, it is

not directed against specific invaders of the body but against any pathogens which enter into the body. Vertebrates have additional and more sophisticated defence mechanisms system, called adaptive immunity, which can recognize and destroy specific substances.

***Immune Response*:** The defensive reaction of the adaptive immune system is called the immune response. Any substance capable of generating such a response is called an antigen, or immunogen. Antigens are not foreign microorganisms and tissues; they are toxins or enzymes in the microorganisms or tissues that the immune system considers foreign. When an antigen enters the body, it may be partly neutralized by components of the innate immune system. It may be attacked by phagocytes or by preformed antibodies that act together with the complement system. For a strong immune system, the body requires energy and nutrients. This depends on what an individual consumes regularly. Moreover, it is important to understand that strong immunity is not built overnight, but by religiously consuming healthy food that has high nutritional value. The immune system protects the body from any kind of bacterial or viral infections by preventing them from invading our bodies (Fig. **2**) [3]. Thus a stronger immune system is an essential means of fighting bacterial or any other viral infections [4].

Fig. (2). The immune system depicting to protect the body from any kind of bacterial or viral infections [3].

CHAPTER 4

The Indian Cytotoxic Weed Flora and Their Phytochemicals

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Abstract: India has rich biodiversity and a large number of medicinal plants that are weeds. Usually, weeds are seen as troublemakers in the yard and interfere with the man's land utilization for a specific purpose. Farmers and field botanists recognized these weeds as medicinal plants such as *Adonis vernalis, Phyllanthus amarus, Eclipta alba, Centella asiatica, etc.* used in folk and indigenous medicines. Most of the plants that are considered weeds have not yet explored phytochemically and pharmacologically. Simultaneously, many of these weeds were reported for their secondary metabolites like alkaloids, glycosides, flavonoids, phenolics, saponins, *etc.* having medicinal values like anticancer, antioxidant, and anti-inflammatory activities. Many therapeutically important weeds are more popular in India, like *Achyranthes bidentata, Artemisia nilagirica*, *etc.* with preferable medicinal benefits such as a diuretic, anti-malarial, and brain tonic. Weeds are storehouses and chemical libraries with simple to complex bioactive secondary metabolites, which serve as drug leads against several resistance diseases like cancer and tuberculosis. Weed biomolecules like Atropine from *Atropa belladonna*, Berberine from *Berberis vulgaris*, Colchicine from *Colchicum autumnale*, Phenoxodiol from *Glycine max*, Ingenol 3-angelate from *Euphorbia* species, Combretatin from *Combre vulgaris* have been reported. This chapter explains various cytotoxic Indian weed flora, reported phytochemicals, drug leads, ethnomedicinal values, modern pharmacology, mechanism of action and clinical safety and efficacy issues.

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Keywords: Anti-cancer, Adonis vernalis, Cancer treatment, Cytotoxicity, Cytotoxic weed, Cancer targets, Centella asiatica, Colchicum autumnale, Combrestatin, Colchicine, Drug, Eclipta alba, Medicinally valued weeds, Phytoconstituents, Phytochemicals, Phyllanthus amarus, Phenoxodiol, Phytochemicals, Secondary metabolites, Weed Flora, Weeds.

INTRODUCTION

On this green planet, there are uncountable plants that are considered wild/weed/unwanted due to a lack of obvious economical value. However, these plants have adapted well to harsh conditions and thrive very well without any special attention. This chapter is focusing on herbaceous weeds which have immense potential in herbal medicine based on traditional knowledge [1]. Around one-quarter of prescription medicines are found to have plant extracts or active ingredients derived from plants. A few essential descriptions of pharmaceutical products extracted from plants are aspirin, atropine, artemisinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine, and vinblastine [2]. However, the search for natural promising anticancer lead molecules is in demand as it is possible to investigate the primary view of structure-activity relationships and its potential mechanism of action from these lead molecules [3].

Significance of Weeds

Weeds are the important and unused components of the agricultural ecosystem, *i.e.*, the right plant in the wrong place. However, weeds are beneficial to humans as food, erosion prevention, drugs, aesthetic value, shelter, organic matter supply, and soil mineral nutrients. The utilisation of agricultural weeds is a widespread problem as some of the plants are characterised by high nutritional value and medicinal properties. There is an extensive awareness that weeds are reasonably rich in bioactive molecules, which is therefore very significant for the development of new medicines [4]. Since the weeds are worthless because of a false assumption, most of these weeds really are not phytochemically and biologically examined, but there are many possibilities for researchers to find new leads toward tough diseases such as cancer [5]. India is a major source of medicinally valuable aromatic plants. Among the high biodiversity range of medicinal plants, this book chapter focused on native ethnomedicinal weeds with documented cancer activities [6].

Basic Insight into Cancer

In evaluating the possible toxicity of research material, whether it be plant extracts or bioactive substances that are derived from plants, the cytotoxic activity

study is helpful in the early phase. Cytotoxicity assays are a quick way to assess a certain chemical compound's impact on a particular human cell line, help to better assess the antineoplastic characteristics of the plant, and could further help to classify novel anticancer compounds [7]. Despite the illness's high profile, its management has been a major challenge with comparatively poor results.

Surgical extraction and radioactive therapy of the massive cumulative biomass of cancer are currently possible alternatives for cancer treatment, usually accompanied by systemic chemotherapy treatment for prevention. Antimetabolites (*e.g.*, methotrexate), DNA-interactive agents (*e.g.*, cisplatin, doxorubicin), anti-tubulin agents (taxanes), hormones, and molecular targeting agents are the majorly accessible chemotherapy medications.

Traditionally, plants are the principal components of the discovery of natural drug ingredients, and plant-derived products like vinblastine and vincristine, etoposide, paclitaxel, taxol, docetaxel, topotecan, and irinotecan are some of the most effective chemotherapeutics widely accessible for treatment of cancer [8]. Numerous significant chemotherapy substances were previously established from natural origins, including such taxanes, some topoisomerase inhibitors, and Vinca alkaloids [9]. Assessing the anticancer potential of these locally available plants brings us one step closer to discovering an alternative source of chemotherapy against cancer [10]. The chapter highlights current trends involved in the discovery of the cytotoxic potential of weeds containing secondary metabolites (Table **1** and Fig. **1**). This chapter was compiled in order to obtain information precisely about Indian cytotoxic weeds.

Phytochemicals used for cytotoxicity Activity from Weeds

Table 1. The reported cytotoxic weed phytoconstituents

Scientific name of the weed	Major constituents	References
Acalypha Indica linn.	Alkaloids like acalyphine, acalyphamide, amides, quinine, sterols, and cyanogenic glycosides, kaemperol, sitosterol, triacetonamine, auranthiamide and its acetate succinimide, 2-methylanthraquinone, tri-o-methylellagic acid.	[1]
Tridax procumbens linn.	Alkaloids, carotenoids, flavonoids like catechins flavones, fumiric acid, oleanolic acid, saponins, tannins, luteolin, glucoluteolin, and quercetin.	[1]
Leucas aspera* (Willd.) *linn.	Alpha-amyrin and alpha-tocopherol, triterpenoids, oleanolic acid, ursolic acid and b-sitosterol, nicotine, sterols, glucoside, diterpenes, phenolic compounds (4-(24-hydroxy-1-oxo-5-n-propyltetracosanyl)-phenol).	[11]
Heliotropium indicum linn.	Heliotrine, lasiocarpine, indicine, 12-acetyl indicine, indicinine, indicine-N-oxide, retronecine, trachelan-thamide, supinidine, and lindelofidine. Echinatine, heleurine, lasiocarpine-N-oxide, supinine, heliotrine, indicine, indicine-N-oxide, and lasiocarpine. Presence of cynoglossine, europine-N-oxide, heleurine-N-Oxide, heliotridine-N-Oxide, heleotrine-N-Oxide, and heliotrine. Other alkaloids such as putrescine, spermidine, homo spermidine, and spermine. Several triterpenes and steroids including b-amyrin, lupeol, chalinasterol, b-sitosterol, stigmasterol and campesterol. Rapanone and hexacosan---ol.	[12]
Cleome rutidosperma linn.	Tannins, lipids, amino acids, flavonoids, cardiac glycosides, alkaloids, steroids, saponins, terpenoids, polyphenols, phlobatannins, pentose, and reducing sugars.	[13]

CHAPTER 5

High Throughput Screening Techniques in Anticancer Drug Discovery and Development from Botanicals

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Abstract: Botanicals obtained from nature are the major source of therapeutic medicines for humans. Utilization of botanicals for a variety of diseases is not mysterious, and a rapid increase in such therapeutic substances is observed due to their efficacy and long-term safety. Cancer, as a leading cause of disease worldwide, piques the interest of researchers seeking novel anticancer agents. Till date, the major share of cancer medicines is occupied by natural products, and the drug discovery process is rapidly going on. However, traditional anticancer drug discovery is time-consuming and herculean. High-throughput screening (HTS) is a tool to make natural product library screening easy and fast. The advancement of extraction, isolation, and structure characterization of Phyto actives obtained from botanicals, provides a large number of compounds for testing *via* HTS. High-density well plates, a liquid handling platform, automation, and robotics allow the screening of 100,000 compounds per day. Anticancer screening of botanicals by HTS can be performed on various cancer cell lines along with molecular targets, enzyme or protein interaction assays, or the capacity of the extract to induce apoptosis. After the replication of identified extracts, further assays are performed for more precise results. HTS screening and computational methods provide speed and a high degree of sensitivity for anticancer agents and compress the time required for drug discovery. Advances in HTS technology, such as ultra-HTS and the use of 3-D cultures, will speed up the process of discovering anticancer drugs from botanicals. Advanced detection techniques for HTS assays, as well as instrumental techniques for identified lead compound separation, help to ensure that the results are neat.

Keywords: Assay, Anticancer, Automization, Apoptosis, Botanicals, Cell proliferation, Dereplication, Drug Discovery, Extracts, High Throughput Screening (HTS), Hit, Lead, Liquid handling platform, Molecular assay, Miniaturization, Natural products, Phytoconstituents, Target identification.

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PREAMBLE

Nature is a mine of medicinal substances obtained from plants, animals, minerals, or marine sources. Products obtained from them remain the major foundation for the treatment of human diseases [1, 2]. A plethora of therapeutic substances have been stored in the womb of nature, among which botanicals are very unique and enormous. Initially, disease treatment was accomplished by using a crude or semi-pure fraction of botanicals, and after the twentieth century, the theory of drug action and receptor link was developed. The thought that drug effects on humans might be due to the interaction of drug substances with biological proteins, nucleic acids, or other macromolecules led scientists to conclude that individual constituents present in such drugs or extracts are responsible for the therapeutic activity of the drug. Eventually, this concept directed the separation of pure bioactive compounds from an extract or drug and the elucidation of their structure [3]. People started to switch over to natural botanicals due to their dissatisfaction with synthetic medicines for the treatment of chronic illnesses like cancer and diabetes. This interest in natural products led to the exploration of more chemical structures, which can be the basis for new drug development, proving that natural products were and will always remain important sources of new pharmaceuticals [4]. It is worth noting that more than half of existing drugs are naturally derived or modified forms of them, with 60% of them being used to treat cancer. This encourages the pharmaceutical industry and academia to focus on developing new drugs from botanicals [2, 5, 6]. Since the isolation of early phytoconstituents such as digitoxin, morphine, cocaine, and codeine, many of which are still in use for various purposes [7, 8], the concept of isolation or fractionation has persisted.

Cancer and Role of Botanicals - Historical Aspects

Cancer is considered a major cause of death worldwide, even after advances in chemotherapy and surgery [9]. In cancer, abnormal cell growth occurs in one place and can spread to other parts of the body, or we can say that it develops when normal cells start to grow abnormally or out of control. There are numerous types of cancer, including those of the blood, breast, lung, prostate, and uterus. Moreover, it is wise to prevent cancer before it requires treatment. Natural products are and will remain an important source of anticancer agents, especially botanicals. Moreover, because they possess a more structurally diverse nature [10] and are associated with less toxicity, it is wise to say that natural product research is a better approach for discovering new anticancer agents. Currently available cancer chemotherapeutics derived from botanicals are vincristine and vinblastine, taxol derivatives (paclitaxel and docetaxel), etoposide, irinotecan, and topotecan [11]. However, they suffer from poor solubility and the associated toxic effects. It

leads to the synthesis of a few analogues and prodrugs of these medicines to overcome drugability issues. In the past many years, natural product drug discovery has gained momentum as researchers have tried to overcome the drugability issues of natural molecules, derive their semisynthetic analogues, and evaluate their efficacies *in vitro*, *in vivo*, and in clinics. Some of the most important anticancer agents are derived from plants, as well as their semisynthetic derivatives, which are widely used. According to Müller-Kuhrt [12], natural products complement synthetic drugs by exhibiting drug-like features. Newer combinatorial approaches for synthesis and computerised methods shifted pharmaceutical industries' interests toward synthetic chemicals for the discovery of new molecules, diminishing the importance of natural products in the drug discovery process. They fear carrying out research on natural products due to the ever-growing competition and time limit, but looking at the architect of natural products and past success utilising newer techniques with fresh strategies helps to overcome this aversion [3]. Table **1** represents some of the botanicals tested for anticancer activity utilising HTS screening techniques.

Table 1. Reported HTS Screening of Botanicals for Anticancer Potential

Sr. No.	Sample Screened by HTS	Biological Source	HTS Assay	HTS Method Adopted	Potent Anticancer Phyto-compounds Identified	Reference
1	Podophyllotoxin (S1, DP1, ET) & Tanshinone (TI, TIIA, TIIB)	*Podophyllum emodi* (Berberidaceae), *Salvia miltiorrhiza* (Lamiaceae)	DNA laddering assay on HeLa-C3 cells	Herrmann's method	DP1, TIIA	[13]
2	Subfraction (SF) 1 to 12	*Albuca setosa* (Asparagaceae)	HeLa cervical cancer cells	MTT viability assay.	C-glucosylflavonoidOglucoside	[14]
3	Approx. 2000 extract prepared from 1220 Brazilian plant	Plants grown in Amazon Rain Forest, Brazil	Breast, Prostate, Lung, Colon, Central nervous system and Leukemia cell lines	SRB colorimetric method	Topotecan, Irinotecan & Camptothecin (Terrestrialsources) and Bryostatin, Dolastatin-10 and Ecteinascidin 743 (Marine Source)	[15]
4	Ethyl acetate-soluble extract	*Ziziphus mauritiana* Lam. (Rhamnaceae)	Human melanoma cells (MEL-2)	Proteasome inhibition assay & Histone deacetylase (HDAC) inhibition assay	Betulinic acid	[16]
5	Chloroform-soluble extract	*Erythroxylum pervillei* Baill. (Erythroxylaceae)	Oral epidermoid cancer cell line (KB-V1)	Proteasome inhibition assay & Histone deacetylase (HDAC) inhibition assay	Pervilleine A	[17]
6	Chloroform-soluble extract	*Aglaia silvestris* (Meliaceae)	Lung, Prostate and Breast cancer cells as well as against Umbilical vein endothelial cells	Proteasome inhibition assay & Histone deacetylase (HDAC) inhibition assay	Silvestrol	[18]

CHAPTER 6

Anticancer Phytochemicals of 21st Century: A Multitargeted Approach and Role of Humanism in Oncology

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Abstract: Unfortunately, we are living in a century where cancer has become an epidemic that is uncontrollable. Although the plant kingdom has been explored for cancer therapeutics due to its antimutagenic, antioxidant, antiproliferative, and alteration of the human immune system potential; these efforts are still underway due to inadequate knowledge of their biochemical mechanisms and molecular pathways. Phytochemicals exert anticancer activity due to their agonistic and antagonistic potentials on different proteins and enzymes involved in the molecular pathways of cancer. This classical phytotherapy treatment has various pitfalls, such as resistance, side effects, and a lack of target specificity. Because of the target-specificity effects, traditional phytotherapy does not distinguish tumour cells from normal cells. A multitargeted approach, in which a single phytochemical act on different points of the same signalling cascade, plays an important role in this regard. Polypharmacology, system biology, and networking pharmacology are the different terminologies to use to explain in detail the multitargeting approach. Classical phytotherapy is replaced with this multitargeted approach where different "omics" such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, and various cytogenic technologies are involved. In this chapter, the various multitargeted approaches involved in cancer therapy and the phytochemicals that were prominent in cancer prevention in the 21st century have been explained. At the end of the chapter, the holistic approach to the treatment of oncology has also been emphasized.

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Keywords: Cancer, Cytogenic technologies, Genomics, Holistic approach, Humanism, Multi targeting, Networking pharmacology, Oncology, Omics, Pathways, Phytochemicals, Polypharmacology, Phytotherapy, System biology, Targets.

INTRODUCTION

In today's world, maybe they are on the path to success, but in fact, there is so much that is out of our control today, and one thing is cancer [1]. Cancer is a community of diseases that alter and spread because of the physiological and metabolic imbalance of cells in the human body. Most cancer cell types eventually form a lump or mass known as a tumor, which is named after the body part where the tumour is located. One of the most multidimensional and complex diseases in the world is cancer, which is a non-communicable disease. Until 2018, the death rate was 9.6 million, and new cases were 18.1 million. According to the WHO, this global disease will be doubled by 2040 (10.108). The primary causes of cancer are environmental (90–95%) and genetic (5–10%), as well as some other lifestyle factors such as the consumption of alcohol, smoking, and junk food. More than 277 cancer types (including prostate, breast, lung, colon, rectum, bronchus, and urinary bladder cancer, *etc.*) have been identified and diagnosed until now. The subtyping of cancer (Fig. **1**) is essential for an enhanced understanding of this complex disease, its diagnosis, and treatment. Cancer disrupts cell connectivity and signaling, which leads to critical gene malfunction. It is a multi-stage process in humans that mimics genetic changes responsible for cancer progression and malignancy [2].

Cancer is now recognised as a multifactorial disorder rather than a single-factor disease [3]. While cancer cells have a complex cellular machinery, the most significant barriers to cancer treatment are cancer tissue regeneration and chemical resistance. This allows researchers to study the widespread use of current drugs in complementary and safe treatment methods to resolve problems in chemotherapy. A multidisciplinary approach with multiple ways of addressing multiple changes in cell signalling machinery that controls expansion, motility, and survival is a viable option [4]. The use of complementary medicines, particularly herbal supplements, is common in cancer patients [5]. Many patients believe that the use of “natural” medicine is efficient and safe.

Since there are many negative effects of anticancer drugs of synthetic origin, it is urgently important to develop safe compounds. In recent years, secondary plant metabolites have become more significant because they may have fewer harmful effects. For many years, oncologists have understood that today's conventional cancer treatment has taken a more individual approach using multiple modalities

[5]. Cancer-friendly agents are more effective in cancer control with multiple targets than agents targeting individual pathways [2]. It is incorrect to say that cancer is incurable, but breast cancer patients also have a very high mortality rate.

Most breast cancers start in the breast tissue of the milk-producing gland, called lobules, or in the conduits connecting the lobules with the nipple. There are fatty, connective, and lymphatic tissues in the majority of the breast [6]. According to the WHO, breast cancer is the most common cancer in women, affecting millions of women worldwide. It is also an advertisement factor. However, because of screening, early detection, sensitivity, and constantly improving care, the death rate has steadily declined since 1990. Age, sex, prosperity, family history, breast disorders, alcohol intake, and obesity are some of the main risk factors for breast cancer [7].

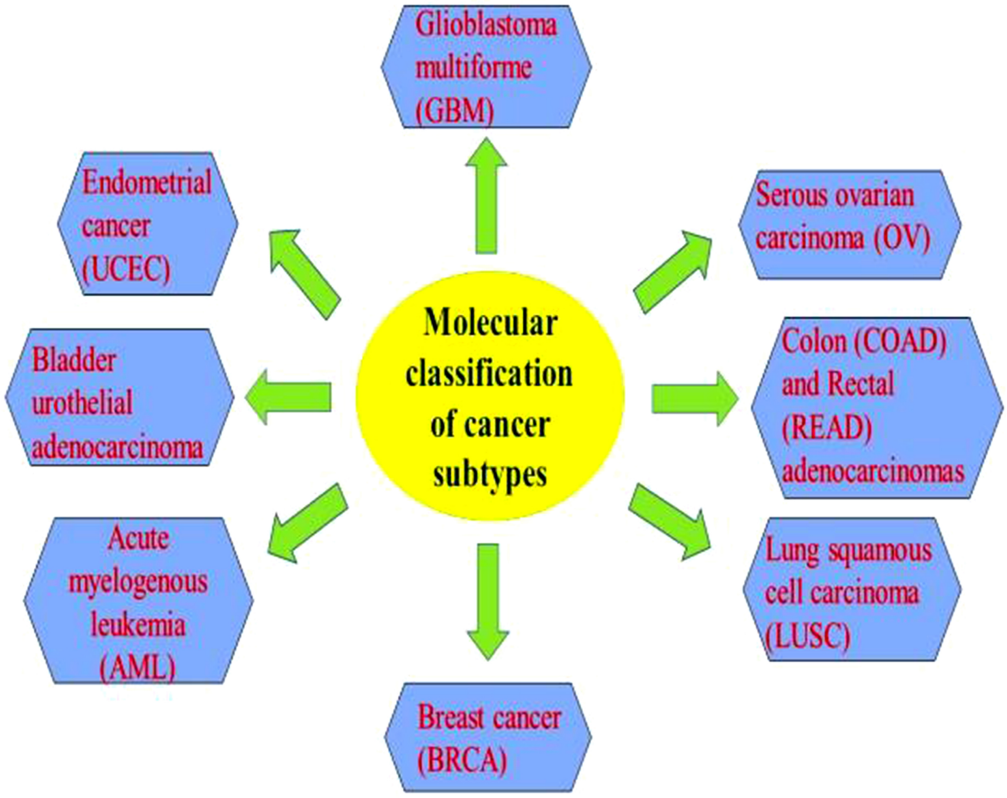

Fig. (1). Molecular Classification of Cancer Subtypes.

The primary cause of cancer was thought to be a variety of mutations throughout various cancer genes, mainly classified as tumour suppressor genes, oncogenes,

CHAPTER 7

Importance of *In silico* Tools in Anticancer Drug Discovery from Nature

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Abstract: Currently, cancer has become one of the most dreadful diseases threatening human health. Natural plant sources play a vital role in the development of several anti-cancer drugs such as vincristine, vinblastine, vinorelbine, docetaxel, paclitaxel, camptothecin, etoposide, teniposide, *etc.* Various chemotherapies fail due to adverse reactions, target specificity, and drug resistance of some types of drugs. Researchers are attentive to developing drugs that overcome the problems stated above by using natural compounds that may affect multiple targets with reduced adverse effects and that are effective against several cancer types. The development of a new drug is a highly complex, expensive, and time-consuming endeavour. In the traditional drug discovery process, ending with a new medicine ready for the market can take up to 15 years and cost more than one billion dollars. Fortunately, this situation has changed with the arrival of novel approaches recently. Many new technologies and methodologies have been developed to increase the efficiency of the drug discovery process, and computational methodologies utilise the existing data to generate knowledge that affords valuable understanding for addressing current complications and guiding the further research and development of new naturally derived drugs. Consequently, the application of *in silico* techniques and optimization algorithms in drug discovery ventures can provide versatile solutions to understand the molecular-level interactions of chemical constituents and identify the hits. Lead optimization techniques such as ligand-based or structure-based drug design are widely used in many discovery efforts. In this chapter, we first introduce the concepts of CADD, *in silico* tools, *etc.* we then describe how this virtual screening has been successfully applied. Furthermore, we review the concept of natural product anticancer therapies

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and present some of the most representative examples of molecules identified through this method.

Keywords: Anticancer, ADME Tool, Bioinformatics, Cancer, CADD, Drug discovery, Drug likeness, *In silico* tools, Ligand, Lead optimization. Phytochemical properties, Molecular docking, Natural anticancer molecule, Molecular dynamics, Pass Tool, Targets, Virtual screening.

INTRODUCTION

Historically, over the years, many natural products from earthly sources have gained popularity for their role in providing better health care and disease prevention. During the early 19th century, Friedrich Serturner, a scientist, performed research on numerous medicinal plants and isolated morphine as an active constituent. This investigation led to the screening of terrestrial natural products for medicinal activity. Over 100 anticancer agents were developed between the end of the nineteenth and the beginning of the twentieth centuries. Out of this, 25 are from natural sources: 9 are purely natural products, 18 are derivatives of natural products, and 11 are derivatives of natural product pharmacophores [1]. The advancement of knowledge and research regarding the prevention and treatment of disease using drugs from plant or animal sources has been observed for years.

Unlike food, cloth, and shelter, medicines are a basic need to fight against illness and to amend mood and consciousness. Natural substances are extremely valued because of their advantageous activities, but modern medicines used nowadays are the advancement of natural products. Hence, a drug used for treatment can be defined as a constituent obtained from either a natural or synthetic origin that is used for the purpose of diagnosing, curing, treating, relieving, or preventing any disease or that is intended to affect the body's function and structure. Thus, a drug is a chemical moiety or compound that affects the body along with its processes. In recent times, a tremendous increase in research on natural products from plant sources has been observed, and they have gained popularity because of their pharmaceutical applications. The phytochemical substances from natural sources produce various molecules with distinctive structures. These molecules tend to produce biological effects through chemical variety and structural complexity.

Nature is the best source of drugs, and it is not very well explored by researchers in the fields of pharmaceuticals, cosmetics, functional foods, and nutritional supplements. Around 25 natural products, like vincristine, vinblastine, docetaxel, paclitaxel, etoposide, teniposide, *etc.*, have been developed for the treatment of cancer and are in various phases of clinical trials. Tools like bioinformatics and

chemoinformatics aid in providing leads and targets. They help in discovering leads against individual targets by using pharmacophores, molecular docking, machine learning, and quantitative and qualitative structure-activity relationship methods. With the aid of molecular docking, quantitative or qualitative structural activity relationships (QSAR), pharmacophores, and machine learning methods, leads can be discovered for targeting.

Most of these approaches have the potential to ease the process of lead discovery against individual targets by using molecular docking, QSAR, pharmacophores, and machine learning methods. Combinatorial approaches, as well as simultaneous interaction with multiple targets, can be used to explore an individual target. 3D target-based methods have their own disadvantages, and 2D structures are better and more reasonable to enable leads for multiple targets. Phytoconstituents obtained from plant extracts are discovered based on their random screening and bioactivity-guided fractionation. The bioactive principle from traditional activities acts as a base for the discovery of drugs with known bioactivities by using molecular docking, and hence, the other natural constituents whose activities are not known are largely unexplored. The activity of those constituents can be determined by using multi-targeted in silico models. Along with chemoinformatics, bioinformatics and system biology approaches are gaining popularity as ways to know the therapeutic activity of medicinally active plants. These methods are used in docking to select the target and identify the relationship between the activity of a phytoconstituent and its therapeutic activity. (Fig. **1**). However, the traditional approach to drug discovery is really time-consuming and cost-intensive. Thus, the new approach to drug discovery exceeds the limitations of traditional research. After studying about 5,000 to 10,000 compounds, only one drug comes to market. Each drug costs about $156 million in the discovery phase. Food and Drug Administration (FDA) processes I, II, and III cost another $75 million. This brings the total to about $231 million for each drug placed on the market for consumers. Then, to gain FDA approval, a long and expensive procedure also needs to be followed.

In recent times, drug design has been carried out with the help of software. Taking into account the fine structure of the target molecule, a whole new ligand is constructed (Fig. **2**). The figure given below is the de novo finding of a lead substance. It has been a powerful tool to build a lead compound.

Drug discovery method: The most important stages of the process of drug discovery in the identification of biologic targets involve the following:

CHAPTER 8

Human Topoisomerases and Caspases: Important Targets in Cancer Therapy

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Abstract: Cancer has always remained a major challenge to humanity with its rising morbidity and mortality rate making it uncontrollable. Current treatments for cancer offer limited efficacy and suffer from serious side effects. With a focus on making treatment safer and more effective, there is a need to identify novel targets and potent drugs for these targets. Recent years have witnessed significant progress in the discovery of targeted cancer therapy. On-going research in this field suggests that human topoisomerases and caspases are important molecular drug targets for anti-cancer drug development. Topoisomerases are DNA processing enzymes essentially required to maintain DNA topology during transcription, replication, recombination and chromosomal decatenation. Several new chemical classes of topoisomerase inhibitors including natural product derivatives are in clinical trials for the treatment of various human cancers. Several topoisomerase inhibitors such as topotecan, irinotecan, camptothecin, teniposide and doxorubicin are clinically approved for various cancers such as colon cancer, lung cancer, breast cancer, and many more. However, many of these inhibitors have also been associated with serious side effects during chemotherapy. Emerging data in recent years also suggests the role of topoisomerase inhibition in immunogenic cell death and activating anticancer immune responses making them potential combinatorial modalities for cancer immunotherapy. Caspases [1-12] belong to the family of cysteine-aspartic proteases responsible for the execution of cell death in apoptotic cells. Caspases play an important role in various non-lethal biological processes like cell proliferation, cell differentiation, intercellular communication, and cell migration. The dysregulation of apoptotic signalling pathways is considered one of the hallmarks of cancer. Hence the focus of cancer therapy is correcting this aberrant behaviour. Natural products such as alkaloids, flavonoids, diterpenoids, sesquiterpenes, and polyphenolics have been reported with various anticancer properties. In this chapter, we have discussed topoisomerases and the regulation of caspase functions through direct or indirect methods for anticancer drug discovery.

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Keywords: Apoptosis, Cancer, Caspases, Chromosomal decatenation, Cysteine-aspartic proteases, DNA topology, Topoisomerases.

INTRODUCTION

Cancer always remains one of the leading health problems globally for many decades, with a growing number of cases and fatalities every passing year. Cancer is the second leading cause of death globally. According to the WHO, an estimated 9.6 million people died in 2018 due to cancer. Available treatment options include chemotherapy, radiotherapy, surgery, immunotherapy, and targeted therapies [1]. Chemotherapy remains the primary approach for cancer treatments. However, the treatment efficiency is limited due to drug-associated toxicities on normal cells and adverse side effects. Therefore, the most effective and less toxic therapy for the treatment of cancer is required. Natural products and their analogues have been reported to demonstrate success in cancer therapy [2 - 5]. Natural products comprise a vast and rich source of bioactive compounds with diverse beneficial effects on our health and living. A lot of safe and useful drugs have been developed based on natural compounds [6, 7]. Scientists around the world are working to find the cure for cancer, wherein topoisomerases I & II and caspases play a very important role in this. In this chapter, we will briefly discuss the role of natural products and natural product-based human topoisomerases inhibitors and caspases modulators towards the therapeutics for cancer.

DNA TOPOISOMERASES

DNA topoisomerases are a group of cellular enzymes that control DNA topology and their proper functioning is essential for most processes taking place in the cell. These ubiquitous enzymes are involved in significant biological processes involving DNA in the cells *e.g.* DNA replication, transcription and recombination or chromosome condensation. To get the genetic information from the DNA it is necessary to separate the two DNA duplex strands and topoisomerases are essential for this and they also enable replicated chromosome release before partitioning and cell division. The utmost necessity of these topoisomerase enzymes is because of the continued need for the DNA duplex to be compacted and fit into a much smaller nucleus. During this process, there are chances for DNA entanglements and knots which can potentially pose serious concerns for the overall DNA functioning. DNA topoisomerases help to overcome these issues. These enzymes work by binding covalently to the DNA phosphorus group, splitting the DNA strand and finally reuniting them. Topoisomerase 1 and Topoisomerase 2 are well-established antitumor drug targets. DNA topoisomerase I was first discovered in 1971 by James Wang, as the omega (ω) protein from *Escherichia coli*. After that, several forms of DNA topoisomerases have been

discovered to date and were characterised in all three domains of life (bacteria, eukarya and archaea). Both human topoisomerase I and human topoisomerase II are targets of anticancer drugs [8 - 12].

Classification and Terminology of Topoisomerases

Depending upon the structures and catalytic activity, there are two main types of topoisomerases: topoisomerases I (Top I) and topoisomerases II (Top II) are further divided into five categories: IA, IB, IC, IIA and IIB. Topoisomerase enzymes terminology is classified according to the number of strands they cut: type I enzymes cut one DNA strand and type II enzymes cut two DNA strands. Depending upon the catalytic activity and structural domain, these enzymes are further divided into three classes; A, B, and C (Fig. **1**). Type I-A enzymes have a tyrosine residue that remains linked to the 5′ end of the cut strand, I-B enzymes have a tyrosine residue that remains linked to the 3′ end and I-C enzymes also have the tyrosine residue that remains linked to the 3′ end. Human topoisomerase I belongs to the type-IB and human topoisomerase II belongs to type-2A topoisomerase [8].

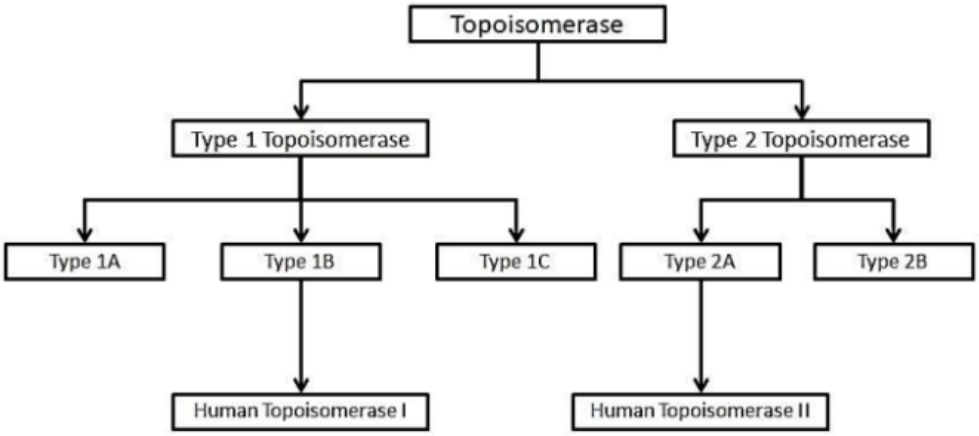

Fig. (1). Classification of Topoisomerases

Human topoisomerase I & II

Human topoisomerase I (hTop I) is a monomeric enzyme that belongs to Type-IB subfamily and has a molecular weight of 91 kDa. It consists of 765 amino acids which form four domains: an N-terminal domain, a linker domain, a core domain and a C-terminal domain as determined by X-ray crystallography [8].

CHAPTER 9

Cytotoxic Phytochemicals from Mushrooms as Potential Therapeutic Agents

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Abstract: Cancer is a collective term for a group of deadly diseases that can affect and spread to various parts of the body. The main feature of cancer is the uncontrolled growth of cells due to a defect in the genes that control normal cell division and growth. As per the latest statistics, cancer is the second-leading cause of death globally, and almost 70% of these deaths are reported in low- and middle-income countries. Chemotherapy and irradiation are the most common cancer treatments; however, the development of resistance and severe side effects are the stumbling blocks of these methods. Hence, current research has focused more on developing novel drug leads from new sources like algae and fungi. Fungi, such as mushrooms, are an inexhaustible source of various anticancer biomolecules, and the 21st century saw a staggering interest in the anticancer potential of mushrooms among the western exploration clique. Their cellular and humoral immunity-boosting properties have made them better candidates for anticancer drug discovery. The mushrooms attributed with cytotoxic potential belong to various genera like *Vargenus Agrocybe, Amanita, Antrodia, Agaricus, Albatrellus Conocybe, Clitocybe, Cordyceps, Clavatia, Flammulina, Funlia, Fomes, Galerina, Gymnopilus, Ganoderma, Hypholoma, Inonotus, Inocybe, Lentinula, Lactarius, Panaeolus, Psilocybe, Plerurotus, Pholiotina, Pluteus, Russula, Suillus, Schizophyllum, Trametes, Xerocomus, and Weraroa.* Hence, the current chapter focuses on the botanical description, phytochemistry, mechanism of action, and clinical status of various vital mushrooms acting as essential libraries of anticancer drug leads.

Keywords: Anticancer, *Amanita*, *Antrodia*, *Agaricus*, *Albatrellus Conocybe*, Cancer, *Clitocybe*, *Cordyceps*, *Clavatia*, Cytotoxic Phytochemicals, Drug leads,*Vargenus Agrocybe*, *Flammulina*, *Funlia*, *Fomes*, *Galerina*, *Gymnopilus*, *Ganoderma*, *Hypholoma*, *Inonotus*, *Inocybe*, *Lentinula*, *Lactarius*, Mushrooms, *Panaeolus*, *Psilocybe*, *Plerurotus*, *Pholiotina*, *Pluteus*, *Russula*, *Suillus*, *Schizophyllum*, *Trametes*, *Xerocomus*, *Weraroa*.

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INTRODUCTION

Cancer is one of the leading causes of death globally. Cancer is estimated to be responsible for approximately one in every six deaths worldwide. As per the National Cancer Registry Programme Report 2020, released by the Indian Council of Medical Research (ICMR), it was estimated that there would be 13.9 lakh cases of cancer in India in 2020, and that this number is probably going to ascend to 15.7 lakh by 2025. Continuous growth and uncontrolled proliferation of cells are the cardinal mechanisms behind the development of cancer. Despite the checkpoints that control a normal cell's behaviour, cancer cells continue to grow and divide in an unregulated manner, affecting and spreading to other organs. More than a hundred recognised types of cancer can differ considerably in their reaction to treatment. Though there are many kinds of cancer, only a few occur frequently, like breast, cervical, prostate, oral, and lung cancer (Fig. **1**).

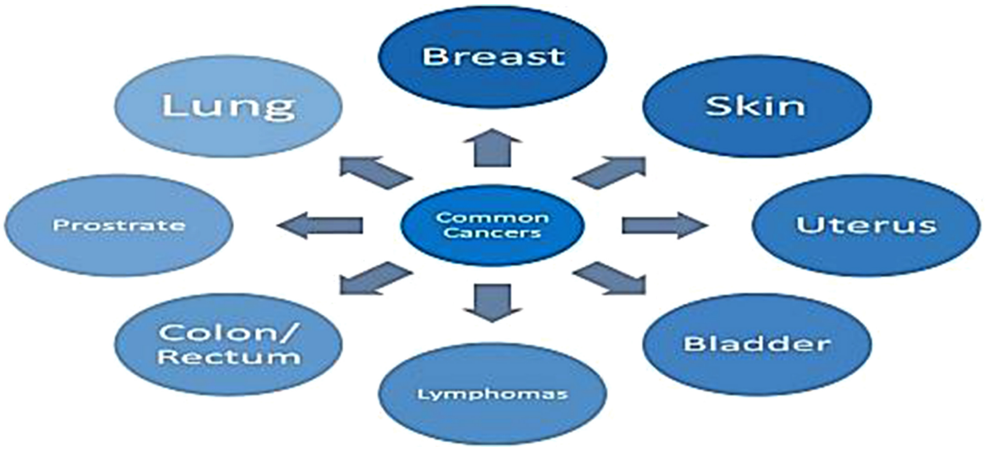

Fig. (1). The Most Common type of Cancers.

The battle against cancer has been reinforced with multidirectional approaches, including behavioural and dietary changes, chemotherapy, radiotherapy, medical procedures, and late immunotherapy. Miserably, these approaches have many ill effects, ranging from a suppressed immune system to decreased patient quality of life. This has encouraged researchers, prompting deliberate endeavours to discover better treatments that, aside from treating cancerous growth, help the immune system fight cancer and other opportunistic infections [1].

Complementary and alternative therapy is one of those therapies mentioned above that use plants, including algae and fungi. Among the enormous resources of fungi, higher basidiomycetes, distinctly mushrooms, constitute inexhaustible

sources of therapeutically active agents [2]. Mushrooms are the spore-producing fruiting body of a fungus that grows above the soil or on a substrate. Several edible and non-edible mushrooms have been used for medicinal purposes since the dawn of civilization. Mushroom derived extracts are predominantly used alone or other herbal preparations to treat various ailments in traditional Chinese medicine (Fig. **2**).

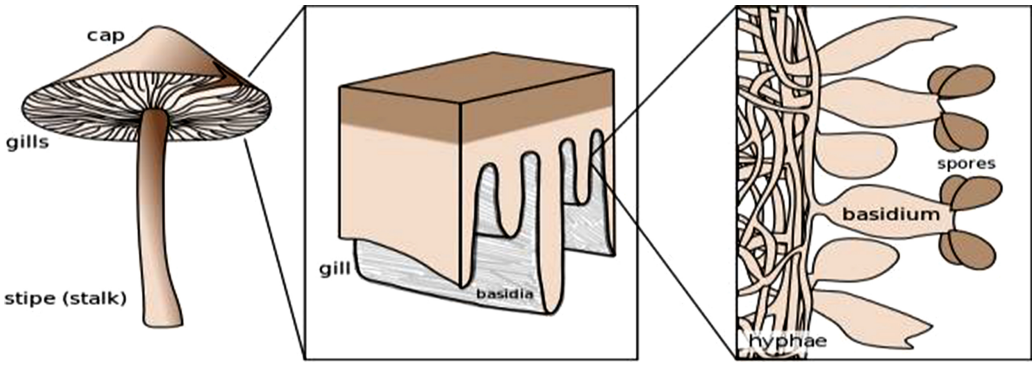

Fig. (2). Basidium Schematic Structure.

Among the enormous resources of fungi, higher basidiomycetes, distinctly mushrooms, constitute inexhaustible sources of therapeutically active agents [2]. Mushrooms are the spore-producing fruiting body of a fungus that grows above the soil or on a substrate. Since the beginning of time, people have used both edible and non-edible mushrooms as medicines. In traditional Chinese medicine, mushroom extracts are mostly used alone or with other herbal preparations to treat a wide range of illnesses. A plethora of biologically active substances, such as polysaccharides, minerals, vitamins, dietary fibers, and polyphenolic compounds, are found in mushrooms. Most ongoing studies have shown that mushrooms have around 130 therapeutic properties, such as antitumor, immunomodulating, antioxidant, cardiovascular, anti-hyperlipidemic, antimicrobial, detoxifying, anti-diabetic, and hepatoprotective [3].

The use of mushrooms in cancer treatment is well known in East Asian countries (Table **1**), the United States, and Canada. These biologically active compounds have been shown to influence the host's immune system and consequently could be used to treat a number of ailments and restore the cell immunity lost through radiotherapy and chemotherapy. But not enough research has been done on the interesting parts of medicinal mushrooms that help treat cancer and their benefits as a cancer support therapy [4].

CHAPTER 10

Spirulina: A Living Library of Anticancer Phytochemicals

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Abstract: Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. It is one of the major causes of human death, especially in developing countries. Alternative cancer treatments using medicinal plants are exploited because plants produce phytochemical compounds, which are secondary metabolites used for natural defence but could also be useful in inhibiting cancer growth. Medicinal plants also have limited side effects and toxicity as compared to conventional chemotherapy and irradiation treatments. Hence there is a need to develop novel drugs from other sources like plants, fungi, and algae. Spirulina is a blue-green alga with three species: *Spirulina platensis, Spirulina fusiformis, and Spirulina maxima. Spirulina platensis* and *Spirulina maxima* are consumable by humans in the form of dietary supplements, as they are enriched with important nutrients and a library of phytochemicals that can improve immunity and levels of blood lipids, lower blood sugar and blood pressure, and prevent oxidation. These activities of Spirulina phytochemicals make them a good candidate for anticancer therapy. Therefore, this chapter describes the botanical classification, phytochemical composition, and anticancer characteristics of Spirulina and with a specific focus on *Spirulina platensis*.

Keywords: Anticancer, Alternative, Blue-green algae, Cancer, Chemotherapy, Chemical library, Dietary supplement, Fungi, Fatty acids, Medicinal, Oxidation, Phytochemicals, Spirulina *platensis*, Spirulina *platensis*, Spirulina *fusiformis*, Spirulina *maxima*, Toxicity.

INTRODUCTION

Cancer is a worldwide major deadly disease that threatens humans' health. A notable treatment for cancer treatment is killing or inhibiting the development of cancerous cells (chemotherapy). However, it is noteworthy that these drugs are associated with toxicity that might be very unpleasant. Recently, increased interest in marine biological resources as sources of bioactive materials has been witnessed, especially in microalgae and seaweeds such as *Spirulina.*

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Spirulina is a microscopic and filamentous cyanobacterium with a simple structure but a complex composition that derives its name from the spiral or helical nature of its filaments. It is a microalga that belongs to the class Cyanophyceae. *Spirulina* refers to the dried biomass of *Arthrospira platensis*, an oxygenic photosynthetic bacterium that can be found worldwide in fresh and marine waters.

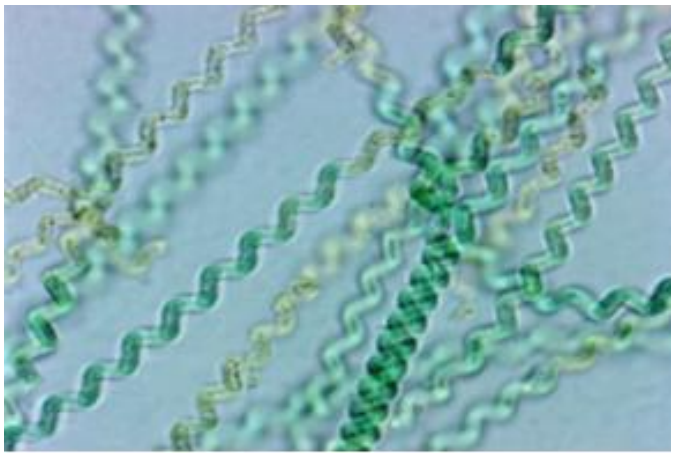

Fig. (1). Filamentous Structure of Cyanobacterium, *Spirulina platensis*

(Source: http://www.spirulinasource.com/library/health-library/)

It lacks cellulose, so it can be easily digested when used as food [1]. It has about 65% protein, 20% carbohydrates, 7% minerals, 5% lipids, 3% moisture, vitamins (B12), pro-vitamin A (-carotenes), and minerals, particularly iron1.Therefore, it is an important staple diet in humans that has been used as a source of protein and vitamin supplements without any significant side effects. Spirulina is rich in phenolic acids, tocopherols, and alpha-linolenic acid [1].

In recent times, the assessment of phytochemicals in macroalgae extracts has greatly contributed to the explanation of their important role in the prevention of human diseases. The identified phytochemicals in the alga are alkaloids, flavonoids, phenols, tannins, phlorotannin, terpenoids, pigments, glycosides, and steroids. These phytochemicals were thought to act as a defence mechanism, protecting them against reactive oxygen species (ROS) resulting from harsh environmental conditions [2, 3]. However, the phytochemicals are useful to humans; for example, Spirulina platensis extract revealed therapeutic cancer prevention activity [4]. As a result of its phytochemical composition, Spirulina thus possesses potent antibacterial, anticancer, antioxidant, antifungal, anti-inflammatory, antidiabetic, neuroprotective, hepatoprotective, and antiviral

properties [5 - 7]. It was stated that most natural substances derived from marine algae have therapeutic and medicinal properties, such as anticancer, antibacterial, and antioxidant properties [8]. Among numerous species of Spirulina, three species, including *Spirulina platensis* (*Arthrospira platensis*), Spirulina maxima (*Arthrospira maxima*), and Spirulina fusiformis (*Arthrospira fusiformis*), are the most widely investigated because they are edible and have high nutritional and medicinal values [9].

Table 1. Nutritional and phytochemical Profile of *Cyanobacterium, Spirulina Powder*

Chemical composition %		**Physical properties**		**Pigments**
protein	60-65	Appearance	Fine powder	Chlorophyll α
Carbohydrates	15-20	Colour	Blue green	c-phycocyanin (C-PC)
Lipid	4-5	Odor and taste	mild like weed	Allophycocyanin (APC)
Minerals	6-7	Particle size	64 mesh through	Phycoerithrin (PE)
Moisture	2-3	Digestibility	83-84%	Cartonese. Betacarotene xanthophyll

(Source; http://www.spirulinasource.com/library/health-library/)

Developing a therapy for cancer treatment without harming the rest of the body is the greatest challenge in designing cancer drug therapy. Therefore, there are many difficulties in the treatment of cancer; these challenges include decreasing treatment-related adverse effects, managing triple-negative breast cancer despite poor outcomes, the lack of a therapeutic target, and balancing treatment toxicity with the quality of life in patients with metastatic cancer who have already received inclusive therapy [10]. To reduce this problem, the use of medicinal plants such as Spirulina platensis has been suggested. Many toxicological studies have proven Spirulina's safety and it has been listed by the US Food and Drug Administration under the category "Generally Recognized as Safe" (GRAS) [11, 12].

Over the past years, studies have discovered new classes of antibiotics or cytotoxic metabolic compounds of microalgae majorly cyanobacteria and green algae [13]. Many crude extracts and compounds obtained from different algae have been estimated for their antitumor activities [14].

The aqueous extract of Spirulina platensis shows pharmaceutical properties, such as the ability to fight cancers, reduce the level of blood cholesterol, decrease nephrotoxicity of drugs and toxic metals, and protect against the harmful radiation effects [15]. The methanolic extract of Spirulina platensis was evaluated against the human breast cancer cell line (MCF-7) and the human cancer cell line L20B,

CHAPTER 11

Terpenoids A Potential Scaffold for Cancer Therapy: A Mechanistic Approach

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Abstract: Cancer remains the most devastating disease that threatens public health with increasing incidence year by year worldwide. The anti-cancer property of naturally derived compounds appears to be a promising approach in cancer therapy. Terpenoids, generally known as terpenes, belong to the most abundant secondary metabolites class and extensively occur in various medicinal plants, fruits, and vegetables. Most of the terpenoids are non-toxic in nature and a ubiquitous part of the human diet. To date, approximately 50,000 terpenoids have been known in nature, and most of them have their use in traditional as well as modern medicinal systems. Based on the number of cyclic structures, terpenoids have been classified into eight main classes such as hemiterpenoids, monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids, and polyterpenoids. Terpenoids have shown several biological and pharmaceutical significances, including anticancer activity. The literature study revealed that terpenoids exhibit anticancer activity against various human cancers *via* inhibiting the initiation and progression of tumor growth *in vitro* and *in vivo*. In addition, many terpenoids inhibit cell proliferation, invasion, metastasis, and angiogenesis which promote apoptosis of various cancer cells *via* inhibiting various deregulated oncogenic intracellular signaling pathways. Moreover, the pre-clinical anticancer efficacy of terpenoids supports their clinical application as an anticancer therapeutic. This chapter attempts to provide a comprehensive overview of recent advancements and mechanistic progress on terpenoids as cancer therapeutic.

Keywords: Apoptosis, Cytotoxicity, Cancer, Diterpenoids, Hemiterpenoids, Monoterpenoids, Oncogenic signaling pathways, Phytochemicals, Polyterpenoids, Sesquiterpenoids, Sesterterpenoids, Terpenoids, Triterpenoids, Tetraterpenoids.

TERPENOIDS

Phytochemicals originated from various traditional medicinal plants, are biologically active compounds, which have a remarkable contribution in the field

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of present-day drug discovery [1]. Many phytochemicals that occur in our diets have been effectively known for their promising disease-preventing properties, including cancer [2]. Terpenoids, very minutely occurring phytochemicals of our diet but highly ubiquitous in nature, are among the largest class of biological agents [2]. At present, over 50,000 terpenoids have been known so far in nature [3]. Interestingly, most of the terpenoids are plant-purified volatile oil-based compounds and mainly occur in medicinal plant groups, including Acanthaceae, Araliaceae, Aristolochiaceae, Celastraceae, Compositae, Labiatae, Lauraceae, Magnoliaceae, Oleaceae, Pinaceae, Ranunculaceae, Rutaceae, Taxaceae, and Umbelliferae [4]. They are highly potent and target selective biologically active compounds, which have been extensively used to combat many deadly diseases. In addition, terpenoids are also known for their several medicinal activities, such as anticancer, antibacterial, anti-inflammatory, antimalarial, and antiviral [4]. Terpenoids also have their uses as blood sugar lowering agents, antiaging agents, immunomodulatory and neuroprotective agents, and in the treatment of many cardiovascular diseases [4]. Studies have revealed that many plant-isolated terpenoids have shown promising anticancer activity *via* inhibiting the initiation and progression of various cancers at an early stage [5]. While they also exhibit significant tumor-reducing potential in the late stages of cancer [5]. Mechanistically, terpenoids inhibit tumor growth *via* targeting various apoptotic and intracellular signaling pathways, cell cycle arrest, anti-angiogenic effect, inhibiting invasion, and metastasis in many types of cancer [6]. Compiling and renewing the recent updates on terpenoids related to an anticancer prospect can provide a newer reference for discovering novel anticancer therapeutics. Thus, this chapter provides recent updates on anticancer activity and diverse mechanisms involved in cancer prevention of terpenoids (Fig. **1**).

DIFFERENT FORMS OF TERPENOIDS

Terpenoids are structurally diverse compounds, and they are synthesized from mevalonic acid (MVA) through the mevalonate or non-mevalonate biosynthetic pathways. MVA is basically derived from different combinations of five carbon structural units (C5) named isoprene. Considering biochemical structural-based studies, terpenoids are mainly categorized into monoterpenoids (C10), diterpenoids (C20), triterpenoids (C30), tetraterpenoids (C40), polyterpenoids (>C40), hemiterpenoids (C5), sesquiterpenoids (C15), and sesterterpenoids (C25). In addition, triterpenoids, sesquiterpenoids, and polyterpenoids are the product of mevalonate biosynthetic pathways, while monoterpenoids, diterpenoids, tetraterpenoids, and sesterterpenoids are derived in non-mevalonate biosynthetic pathways. However, isopentenyl pyrophosphate (IPP) is a common precursor in synthesizing all forms of terpenoids. It has been observed that continuous polymerization of IPPs by the enzyme prenyltransferases yields prenyl

pyrophosphates (terpenoids skeleton). Finally, in the third phase, another enzymatic modification in prenyl pyrophosphates resulted in functional terpenoids.

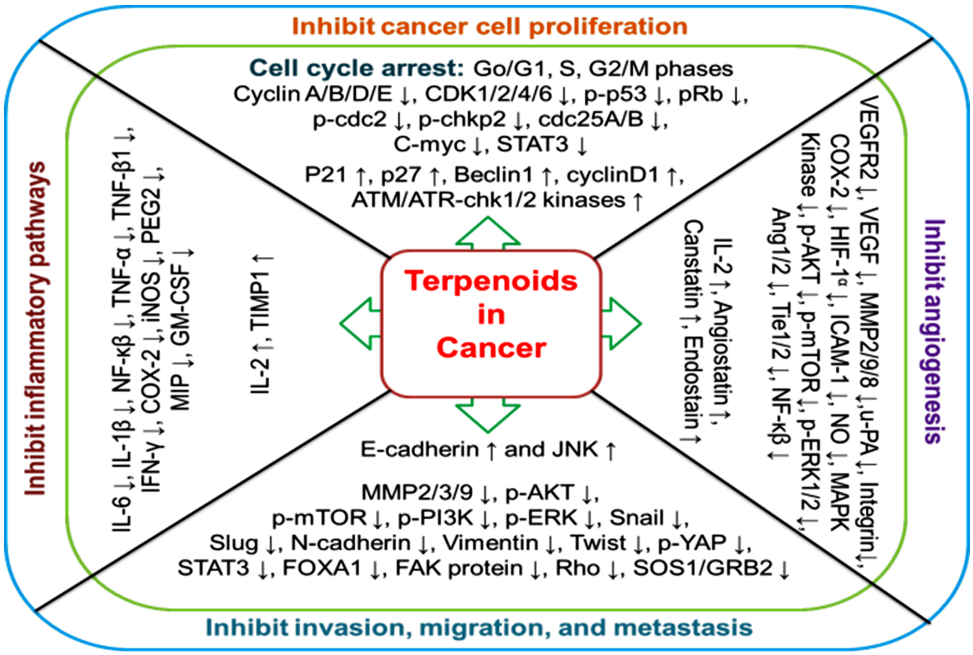

Fig. (1). Terpenoids regulated diverse mechanisms in cancer prevention.

Monoterpenoids

Monoterpenoid (C10) is the combined product of two isoprene residues with molecular a formula C10H16. They can be further classified into mono-, bi-, and a-cyclic groups. Monoterpenoids are mainly obtained from essential and fixed oils naturally occurring in plants. Monoterpenoids are well-known for their use in making perfumes due to their strong aroma and fragrance. In addition, they have shown vital biological activities, such as anticancer, anti-inflammatory, and antibacterial activity. For example, a monoterpenoid, Geraniol, shows a significant growth inhibitory effect against human hepatic carcinoma cell line HepG2 [7]. Mechanistically, the molecular target of Geraniol was 3-hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in the biosynthesis pathway of cholesterol. Geraniol showed a growth inhibitory effect by inhibiting the expression of HMG-CoA-reductase in the HepG2 cell line [7]. The chemical structure of some monoterpenoids is shown in Fig. (**2**).

CHAPTER 12

Cytotoxic Phytochemical library of *Rosmarinus Officinalis*

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Abstract: Globally, the prevalence of cancer has escalated at an alarming rate, and it has become a major health problem. The World Health Organization reported that one in six deaths is due to cancer. Despite the advantages of current chemotherapy available for cancer treatment, the development of resistance and severe side effects continuously insist cancer research focus on the discovery of new entities, especially from natural sources. In the last few decades, varieties of dietary herbs have been explored for their cytotoxic potential. Rosmarinus officinalis, a well-known culinary herb commonly known as rosemary, is not only used to enhance the flavour but also possesses medicinal values. The Rosmarinus officinalis plant extract and its essential oil are packed with different phenolic acids and terpenoids. Rosmarinus officinalis has anti-cancer, anti-proliferative, protective, anti-inflammatory, and anti-oxidant properties, according to several *in vitro* and *in vivo* studies. The antitumor activity of Rosmarinus officinalis is correlated with different molecular mechanisms such as reactive oxygen species scavenging, the on-co-suppressor gene expression, apoptosis, and immunomodulatory response regulation. So this chapter mainly focuses on the cytotoxic activities of Rosmarinus officinalis and the molecular mechanisms responsible for their anticancer activities. Also, possibilities of utilising the extracts, essential oils, and phytochemicals of Rosmarinus officinalis as potential therapeutic agents or complementary therapies with chemotherapeutic agents for cancer treatment have been discussed.

Keywords: Anticancer, Cancer, Cytotoxic Phytochemicals, Molecular mechanisms, Rosemary.

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INTRODUCTION

Cancer is still continued to be a global burden that causes physical, emotional and financial strain on individuals, families, communities and health systems. In 2018, 9.6 million deaths and 1 in 6 deaths were reported due to cancer and it is the second leading cause of death worldwide. Leukemia, colorectal, prostate, lung, stomach and liver cancer are the most common types of cancer in men, while breast, lung, cervical, colorectal, and thyroid cancer are the most common among women. Blood cancer, and cancers related to the brain and lymph nodes are observed in children (Fig. **1**) [1].

Due to the prevailing resistance and side effects of anti-cancer agents, there is a need for the development of newer anti-cancer entities from natural sources like plants, algae and microbes. Many studies have been focused on developing newer anti-cancer drugs or leads from plant sources [2].

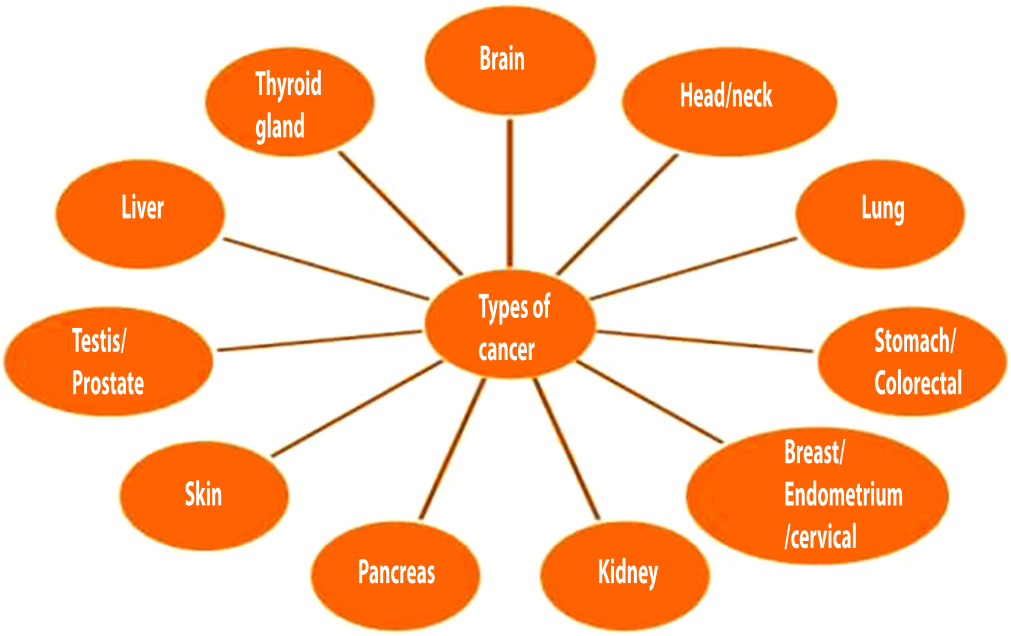

Fig. (1). Common types of cancer

Rosmarinus officinalis, commonly known as "Rusmari," belongs to the family Lamiaceae. This evergreen shrub is native to the Mediterranean and Portugal and grows all over the world. It grows 1-2 m high and has hard, narrow-linear, needle-shaped leaves that are packed with essential oil in their glandular scales. The tiny, two-lipped, bluish Labiatae flowers grow on the upper part of the branches. When

rosemary leaves are crushed, they emit a camphoraceous and pungent aromatic odor.

The strong fragrance of this shrub is widely used in culinary flavoring, cosmetics, and toiletries. It was once used to expel negativity, improve memory, and season food. It is also believed that the benefits of rosemary are associated with the treatment of brain, liver, and eye problems, and that it has a wide range of therapeutic activities such as anticancer, cytotoxic, anti-inflammatory, anti-diabetic, anti-nociceptive, anti-microbial, diuretic, and hepatoprotective activities [3 - 9].

Taxonomy of *Rosmarinus officinalis*:

Domain: Eukaryota

Kingdom: Plantae

Phylum: Spermatophyta

Subphylum: Angiospermae

Class: Dicotyledonae

Order: Lamiales

Family: Lamiaceae

Genus: Rosmarinus

Species: Rosmarinus officinalis

Fig. (2). *Rosmarinus officinalis*

CHAPTER 13

Cannabis in the Treatment of Various Cancers and its Current Global Scenario

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Abstract: Cannabis has been used as a drug for centuries, possibly much longer before it was recognised as an illegal substance. The prime psychoactive property is marked on the 9-THC compound. The cannabinoids replicate the action of endocannabinoids by stimulating receptors in the central nervous system and lymphatic system *via* diligent CB1 and CB2, respectively. Cannabinoids, on the other hand, are well known for their dependency, which is less severe than that of other drugs that can be abused. Cannabis' anti-tumor and anti-cancer potential was only discovered at the turn of the twentieth century. Cannabis consumption has been reported to benefit patients with cancer by suppressing nausea, curbing vomiting, elevating appetite, alleviating pain, and pacifying anxiety. Studies envisage that the up-regulation of CB receptors and their associated endogenous ligands correlates with the suppression of tumours. Patients have found cannabis to be effective in reducing side effects and relieving pain when used in conjunction with chemotherapy. Though cannabis prescription is restricted under federal laws in many countries, its lucrative efficacy profile has pushed regulators to reconsider its use in medical causes such as cancer. This chapter is an attempt to emphasise the biological role of cannabis in cancer pathophysiology.

Keywords: Anticancer effect, Cannabis, Cannabinoids, Endocannabinoid , THC.

INTRODUCTION

Cannabis, often referred to as European hemp, is mainly composed of the dried shoots of female plants in blossom condition, specifically Cannabis sativa, Cannabis indica, and Cannabis ruderalis, which are commonly found in India, Pakistan, and Bangladesh. Since 500 BC, Asian traditional medicines have used Cannabis sativa plant extract. Cannabis contains about 300 compounds categorised as cannabinol, cannabidiol, and tetrahydrocannabinol (cannabinoids), consisting of an aromatic portion (C11 or C12), theoretically derivable from six acetate units, and an isoprenoid component [1, 2].

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Cannabinoid receptors were discovered much later in humans than in the endocannabinoid system. The theory of non-specific receptor activation for cannabinoids' bioactivity in animals was rejected in the late 1980s when experiments on a rat model characterised specific cannabinoid receptors, CB1 and CB2 [3]. Recent studies suggest that the CB1 receptor is active in the central nervous system (CNS), whereas hematopoietic cells show expression of the CB2 receptor [4]. Endogenous ligands for the CB1 and CB2 receptors, 2-arachidonolyglycerol (2-AG) and N-arachidonoylethanolamine (AEA), have an affinity for groups of G protein-coupled receptors (GPCRs) linked to endocannabinoids and provide relevance of their bioactivity [5, 6].

Recently, the treatment of cancer included cannabinoids after mysterious studies showed the development of CB1 and CB2 receptors in cancer cells, which were responsible for tumour suppression. The hypothesis was confirmed by the characterization of overexpressed CB1 receptors in hepatocellular carcinoma, Hodgkin lymphoma, and epithelial ovarian carcinoma [7 - 11]. Similarly, CB2 has also been found to be overexpressed in HER2+ breast cancers and gliomas [12]. Carchman and co-workers proved the anti-tumor activity of cannabinoids *via* inhibition of DNA synthesis in lung adenocarcinomas, gliomas, breast, pancreas, and prostate lymphomas *in vitro* and *in vivo* models.

The above-reported research has many proposed mechanisms of action, including cell cycle arrest, induction of apoptosis, inhibition of neovascularization, migration, adhesion, invasion, and metastasis. In spite of so many positive findings that support the use of 9-THC-related cannabinoids in cancer research, these compounds are not used clinically because of their psychoactive side effects. The affinity of CBD towards receptors is still questionable [5, 13, 18]. CBD is also reported to interact with other cellular receptors, namely TRPVs, 5-HT1A, GPR55, and PPAR, leading to strong anti-proliferative and pro-apoptotic activities. Besides this, it is also postulated to inhibit the process of metastasis [14 - 17]. The discussion will continue on the anti-tumor activity of CBD, which is linked with the regulation of cell parameters such as ROS, ER stress, and immune modulation, among other probable mechanisms.

Anticancer Effects of Cannabis in the Following Cancers

Glioma

Glioma, or glioblastoma multiforme (GBM), is the most common and hostile type of brain tumour [19]. The GBM remains undetected for up to 5 years, and the rate of survival is reported to be only 4–5% within this period [19]. Most clinical cases are treated with a combined approach of surgery and radiotherapy; however, che-

-motherapy with Temozolomide or Carmustine is necessary to restrict the growth of cancer [20].

Treatment for GBM management is challenging to treat urgent medical needs, hence many scientists' have extended the use of cannabinoids. CBD in combination with other neoplastic drugs showed better cell apoptosis due to the upregulation of TRPV2 receptors, increased *in vitro* inhibition of cell invasion, and decreased *in vivo* angiogenesis, which induce tumour regression [20 - 26]. Ivanov *et al.* establish a link between CBD use, -irradiation, and neoplastic agents in terms of activation of TNF/TNFR1 and TRAIL/TRAIL-R2 for apoptotic pathway fulfillment [27, 28].

Literature suggests that CBD activates apoptotic pathways in glial cells. However, no evidence was found for the role of CBD in glial cell cycle arrest, hence its use as a secondary therapy for patients with high-grade gliomas [29, 30]. The oral administration of CBD along with key players in GBM management such as procarbazine, vincristine, lomustine, *etc.* showed mild adverse effects like rash, nausea, and fatigue, but there were no signs of any lymphopenia, thrombocytopenia, hepatic toxicity, or neurotoxicity [31]. An important study on nine volunteers with grade IV GBM found that a higher dose of CBD (200–400 mg/day) resulted in a prolonged tumour arrest period and no signs of disease progression for three or more years. In conclusion, we must say the results indicate that CBD alone or in combination with routine treatment for GBM shows great promise with relatively mild side effects [25, 27].

Breast Cancer

Breast cancer is the most common type of cancer worldwide. Since 2006, the effects of CBD on breast cancer have been examined, and research in this area has recently expanded [32]. Estrogen receptor (ER)-positive cells (MCF-7, ZR-75-1, and T47D), ER-negative cells (MDA-MB-231, MDA-MB-468, and SK-BR3), and triple-negative breast cancer (TNBC) cells (SUM159, 4T1up, MVT-1, and SCP2) all showed a dose-dependent response to CBD. Very significant results were observed with such a low dose of CBD in MDA-MB-231 after 24 h [26, 33].

As a result, the CBD's IC50 values for the vast majority of cell lines were inadequate. This was a demonstration that CBD's anti-proliferative properties are often responsive to breast cancer cell lines. However, CBD would have no effect on stable breast epithelial cells [34]. The mechanism for the action of CBD on breast cancer progression is limited to apoptosis, autophagy, and cell cycle arrest only. *In vitro* studies of CBD on cell lines such as MDA-MB-231 and MCF-7 showed apoptotic response *via* regulation of caspase-3 and cell cycle arrest at the G1/S phase respectively.

CHAPTER 14

Modern Nanotherapeutic Approaches in The Delivery of Phyto Pharmceuticals in Anti Cancer Research

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Abstract: Cancer has become one of the leading causes of human morbidity and mortality worldwide. A promising approach to tumour prevention is to eliminate cancer cells, preferably with less harm to neighbouring normal cells. Due to the disadvantages associated with current chemotherapy and radiation therapy, there is an increasing interest in developing novel delivery strategies for these natural products. Many phytochemicals show promise in cancer prevention and treatment due to their biocompatibility, low cytotoxicity, low resistance, and dynamic physiochemical properties that discriminate normal cells in the treatment of various cancer types. However, their low aqueous solubility, poor stability, unfavourable bioavailability, and low target specificity make their administration at therapeutic doses unrealistic. Recently developed nanotechnology has transformed drug delivery concepts and paved the way for the development of phytochemical-loaded nanoparticles for cancer prevention and treatment. Polymeric nanoparticles, lipid nanoparticles, carbon-based nanoparticles, and cell-derived nanoparticles can increase the stability and solubility of phytochemicals and also help in overcoming the disadvantages associated with conventional chemotherapy and phytochemicals. In the current chapter, we have men-

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tioned the importance of nanotechnology in the delivery of phytochemicals and also added a note on the significance of delivery with current chemotherapeutics, including present challenges and future perspectives.

Keywords: Cancer, Chemotherapy, Cell cycle, Co-delivery, Checkpoints, Carbon nanoparticles, Drug delivery, Exosomes, Lipid nanoparticles, Nanoparticles, Phyto- chemicals, Phytomedicine, Polymeric nanoparticles.

INTRODUCTION

Cancer is one of the leading causes of death across the world. In 2018 alone, there were around 18.1 and 9.5 million new cancer cases and cancer-related mortalities, respectively. It is anticipated that there would be 29.5 and 16.4 million new cancer cases and cancer-related mortalities, respectively, by 2040. Cancer incidence is often higher in countries with a higher life expectancy and standard of living. According to statistics from 2015–2017, cancer would be diagnosed in approximately 39.5 percent of men and women at some point in their lives. In 2020, a projected number of 16,850 children and adolescents aged 0 to 19 would be diagnosed with different types of cancer, with 1,730 dying from cancers.

In 2018, the expected national cancer care expenses in the United States were $150.8 billion, and the costs are likely to climb in the coming years with the progression of age. As a result, enhancing overall survival and maintaining the quality of life are always necessary in order to reduce the worldwide burden of cancer. Future work will focus on improving current treatment options through dosing regimen optimization and the creation of successful chemotherapeutic combos.

Cancer Biology and Cell Cycle Checkpoints

The cell undergoes different phases for the evolution of new cells, which is generally called the “cell cycle.” The cell cycle was divided into different phases and events. G1 phase, S phase, G2 phase, and M phase are the different phases undergone by the cell, which will give rise to two daughter cells, and again that cell will undergo the cell cycle process, and the process continues. In the cell cycle process at the G1 phase, the cell prepares to divide and then moves to the S phase, where the DNA and genetic material are copied by the cell, and then to the G2 phase, where the genetic material is organised by the cell, and finally to the M phase, where the cell undergoes mitosis, where the genetic material is divided, and two daughter cells are formed [1]. External and intracellular factors will influence and control the cell cycle progression by interfering with the

cyclin/CDK task, resulting in a cell cycle pause, which is also known as a "checkpoint." In this case, the cells are given time to repair the damaged DNA, and various levels of growth factors are obtained to transfer the genetic material to the next phase. If severe damage has occurred to the DNA, it will start the

apoptotic signalling cascades to stop the damaged DNA from inhibiting its replication and further passage to the next phase of the cell cycle [2] (Fig. **1**).

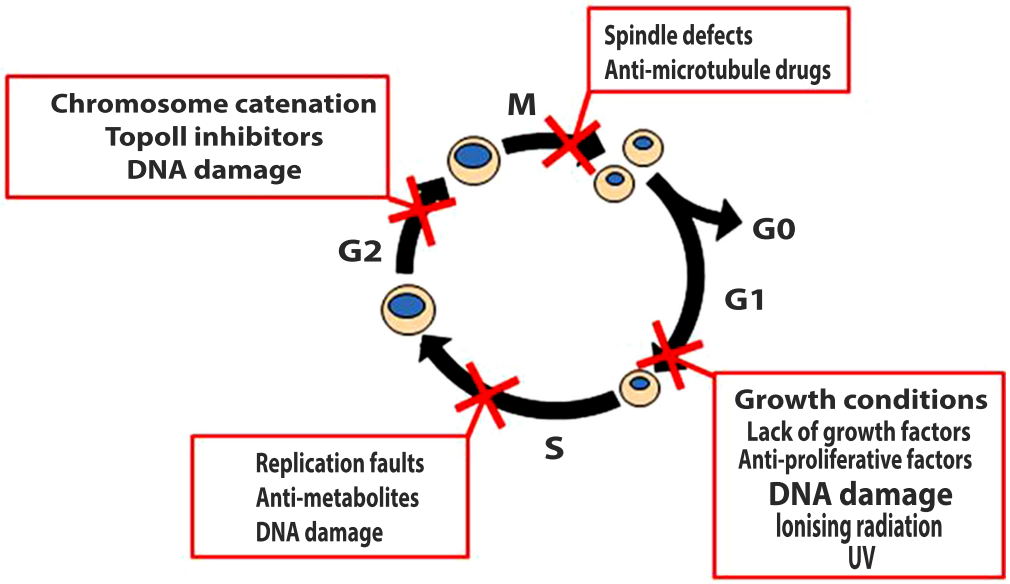

Fig. (1). Cell cycle Check points, reproduced from Gabrielli B, Brooks K, Pavey S. Defective cell cycle checkpoints as targets for anti-cancer therapies. Frontiers in pharmacology. 2012 Feb 2;3:9, under the terms of the Creative Commons Attribution Non Commercial License

During cell cycle, four major checkpoints have been identified: the restriction check point (G0/G1), the G1 check point, the G2 check point, and the mitosis-associated spindle-associated check point (SAC). The G0/G1 checkpoint is present in the G1 phase, which is controlled by the Rb/E2F signalling pathway. The E2F transcription factors were released from the Rb, which activates the genes and initiates the replication of DNA, which then enters the S phase. If the upstream regulators of Rb and the inactivating mutations present in RB1 are overexpressed, the degradation of this check point occurs, and early activation DNA occurs. Delayed DNA replication during the G1 checkpoint results in DNA damage.

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Motamarri Venkata Naga Lalitha Chaitanya

Prof. Motamarri V N.L. Chaitanya ; Ph.D. in pharmacognosy. He is an educationist and a researcher in industry, academia, and herbal research. He is currently working as an associate professor in the School of Pharmaceutical Sciences at the Lovely Professional University, Phagwara, Punjab, India. He is a well-recognized conceptualist in herbal medicine, anticancer drug discovery and development, crystal healing, and psychic reading at the Indian and African levels. He has a keen ability in laboratory drug discovery and development from herbs, weeds, algae, and mushrooms, with a proven ability in quality documentation.

Galvina Pereira

Dr. Galvina Pereira specializes in Medicinal Natural Products. She has five years of research and seven years of academic experience, including extraction, isolation, and quantification of natural molecules. She has developed technologies for the extraction and isolation of 4 phytoconstituents, which are now commercialized via Tech-transfer. Her expertise includes stability, stress degradation, structure elucidation, semi-synthesis of phytoconstituents, downstream processing of biosimilars, and protein purification.

Heyam Saad Ali

Prof. Dr. Heyam Saad Ali, Ph-D., Professor in Pharmaceutics Department (HOD), University of Khartoum, Sudan, contributed more than 70 articles to reputed international scientific journals and conferences different conventional, controlled, and targeted drug delivery systems in pharmaceutical product development. She has been invited as a speaker at numerous international conferences. Reviewer and member of the editorial board of many international journals. My significant research interest is in conventional and advanced drug delivery systems, transdermal drug delivery systems, bioavailability & bioequivalence. Cosmetic products, science, formulation stability, clinical applications, and validating alternative delivery systems using modern pharmaceutical