FUNCTIONAL FOODS FOR HEALTH MAINTENANCE: UNDERSTANDING THEIR ROLE IN CANCER PREVENTION

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CONTENTS

FOREWORD

I feel privileged to write a foreword for this book that addresses the potential of natural product-derived nutraceuticals in the prevention and treatment of cancer and examines the techniques and methods employed for detecting their mechanism of action at the molecular and cellular level. Considering that cancer incidence and associated mortality and morbidity are increasing worldwide, accompanied by spiraling treatment and healthcare costs, strategies for the prevention of the disease are becoming very important. Many approaches have been implemented to reduce the incidence of this dreadful disease, but the use of natural chemopreventive agents remains, in my opinion, a promising and cost-effective strategy. Furthermore, natural product-derived chemopreventive agents are expected to be free of undesirable toxicities. Non-invasive methods for cancer detection, screening, diagnosis, treatment and metastasis are also of paramount importance in cancer chemoprevention. These methods are also addressed in this book titled "Functional Foods for Health Maintenance: Understanding their Role in Cancer Prevention" edited by Dr. Saroj Arora, Dr. Tajinder Kaur, Dr. Rajendra Mehta, Dr. Balbir Singh and Dr. Sandeep Kaur.

The book covers a broad range of topics contributed by experts in their field. Among them, it includes comprehensive overviews of nutraceuticals, phytochemicals, the application of nano-technology in cancer chemoprevention, and the techniques used for monitoring treatment outcomes. The book presents several studies that comprehensively demonstrate that nutraceuticals have anti-cancer properties. Understanding the mechanism of action of these natural chemopreventive agents is essential for the selection of the most promising combinations for maximum efficacy. Generally, chemopreventive agents modulate or disrupt the molecular mechanisms driving the process of carcinogenesis, including (a) preventing or reducing DNA damage introduced by reactive oxygen species in normal cells, (b) blocking cellular signal pathways involved in cell cycle progression and proliferation in cancer cells, and (c) promoting apoptosis in cancer cells.

I congratulate the editors for compiling this publication that provides the reader with the most recent advances in cancer chemoprevention and explains the use of nutraceuticals and functional foods in health maintenance. I expect that scientists interested in cancer treatment and prevention within the fields of cancer biology, biochemistry, pharmaceutical sciences and biotechnology will find this book very useful.

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PREFACE

Cancer is a complex genetic disease which accounts for more than eight million deaths and roughly fourteen million new cases each year, inspite of the modern advancement in medical therapeutics in the world. Several evidences have shown that the plant-based foods consumption lower the risk and incidence of cancer and other degenerative diseases. Phytochemicals as secondary plant metabolites possesses antioxidant activity by inhibiting DNA damage induced by oxidative stress and thereby play crucial role in cancer chemoprevention. In contrast, the pro-oxidant activity of these phytochemicals/nutraceuticals has been found in the treatment of cancer in which they modulate cellular processes undergoing molecular alterations involve in the development of cancer. Furthermore, *in vivo, in vitro* and *ex-vivo* studies and the techniques employed for the diagnosis of cancer have been fully capable to expose phytochemicals having distinct impact on the prevention and treatment of cancer and other diseases.

The present book "*Functional Foods for Health Maintenance: Understanding their Role in Cancer Prevention*" summarizes the evidences, methods and techniques focused on identifying specific nutraceuticals capable of interfering and reducing the risk of cancer and other diseases development along with their underlying molecular mechanism. It contributes an up-to-date information and understanding in the context of interaction between nutraceuticals as chemotherapeutic agents and cancer progression which is a crucial contemporary discovery. Chapter one provides an overview of spices, herbs, fruits and vegetables used as medicine and studied as an important source for cancer chemoprevention. Chapter two shows that dietary intake of *Allium* species reduce the risk of cancer and have significant antitumor activities. Chapter three to ten mainly deals with the chemomodulatory effects of phytochemicals/nutraceuticals along with their varied action mechanisms including inhibition of gene expression, promotion of apoptosis of cancer cells, antiproliferative activity, anti-oxidant and anti-inflammatory effects. Chapter eleven elucidate the pharmacological properties of biomolecules derived from marine algae to provide baseline information for promoting anticancer research. Chapter twelve to sixteen comprehensively deals with the biomarkers, methods and models playing crucial roles in screening, asymptomatic and early stage detection, monitoring of the treatment therapy of cancer. Chapter seventeen highlights the role of nanotechnology in functional foods in order to enhance their bioavailability, absorption and biological activity. Chapter eighteen discusses the biological activity of nutraceuticals for the prevention and therapy of several diseases and its market demand because of increasing consumer knowledge of these compounds.

We express our gratitude to all the contributors. We would like to thank Prof. (Dr) Andreas Constantinou for writing foreword. Finally, it is a profound pleasure to thank Bentham Science for taking up the publication of this book. We hope that this book will provide recent scientific knowledge on chemotherapeutic potential of natural products and the techniques employed for the detection of cancer and other diseases and will lead to new discussions about the global scope of nutraceuticals.

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CHAPTER 1

Unravelling the Role of Vegetables, Pulses and Spices as Therapeutic and Chemopreventive Agents

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Abstract: Worldwide, cancer has become the most life-threatening disease. The current remedial treatment of cancer includes chemotherapy, surgery, immunotherapy, stem cell transplant and hormone therapy. Plants produce secondary metabolites in abundance having medicinal properties used for treating various diseases, such as AIDS, diabetes, cancer, inflammation, fever, diarrhoea and bacterial and fungal infections. Naturally derived components are largely considered by scientists and researchers due to their low toxicity and lesser side effects. Functional foods are the food or food components that provide health benefits beyond basic nutrition. Functional foods simply provide nutrients that help to maintain health, thereby reducing the risk of disease. Various vegetables like *Asparagus racemosus, Cocos nucifera, Brassica oleracea var. Botrytis, Zingiber officinale, Atrocarpus heterophyllus, etc*., pulses, *i.e*., *Cicer arietinum, Phaseolus vulgaris, Vigna radiate, Vigna mungo, etc*., and Spices *viz., Ferula asafoetida, Piper nigrum, Elettaria cardamomum, Coriandrum sativum, Nigella sativa* and *Curcuma longa*, are explored for their potential role to fight many diseases and anticancer activity. This review aims to highlight the protective and synergistic role of functional foods in cancer prevention.

Keywords: Anticancer activity, Chemotherapy, Hormone therapy, Immunotherapy, Life-threatening disease, Secondary metabolites, Surgery, Stem cell transplant.

INTRODUCTION

Cancer is one of the most deadly or life-threatening diseases that critically affects the human population [1]. Cancer is described as a disease in which the formation

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of abnormal cells grows destructively by overlooking the natural process of cell division [2]. There are more than 100 different types of cancers that occur due to some molecular variance in the cell [3]. The known types of cancers in India are blood, stomach, bladder, lungs, breast, liver, prostate, mouth, skin, cervix, rectum and oesophagus cancer. The International Agency for Research on Cancer (IARC) concluded cases of leading types of cancer. In 2030, there will be nearly 26 million fresh cancer patients and 17 million deaths per year [4]. Conventional methods like chemotherapy could cause undesirable and lethal side effects on normal cells while treating infected cells. The use of natural plants is an alternative key to the destructive effects of synthetic agents. Natural products are considered conventionally a rich source of phytochemicals that possess potent bioactivities against chronic diseases like cancer, diabetes and infectious diseases [5]. World Health Organization states that about 80% of people living in rustic areas depend on the herb as a prime healthcare system because of cost factors and easy availability [6].

ANTICANCER ACTIVITY OF PLANTS

About 187 plant species, 102 genera and 61 families provide active sources of various phytoconstituents having anticancer activity, interrelating to a 41% rise from the past 5 years [7].

Plants are the most reliable source for various disease treatments. More than 60% are of the natural origin, of which the maximum is picked up from higher plants. The active principles collected from different plants, such as *Solanum tuberosum, Prunella vulgaris, Aloe vera, Vinca rosea, Glycine max, Allium sativum, Glycyrrhiza glabra, Cucurbita maxima, Tinospora cordifolia* and *Zingiber officinale* and many more are greatly utilized in various pharmaceutical preparations to upgrade the activity of immune cells of our body that stimulate the growth of cytokines in addition to interferon, colony-stimulating factor, interleukin and tumour necrosis factor [8]. Different herbs, fruits and vegetables are used as medicine and studied as an important source for cancer chemoprevention drug discovery and development [9].

DIETARY SUPPLEMENTS OR NUTRACEUTICALS

Nutraceutical is a word made by combining two words, ‘nutrition’ and ‘pharmaceuticals’. Nutraceutical may be defined as food or maybe a part of food that acts significantly to recast and control the normal physiologic behaviour of human beings to maintain their good health [10]. Nutraceuticals are made to prevent various chronic diseases of human beings. They cure or inhibit disorders which are related to oxidative stress, *e.g*., cardiovascular diseases, allergies, hypo- and hyper- glycaemia, inflammation, alzheimer, cancer, Parkinson’s disease, and

eye and immune disorders [11]. Around 2,500 years past, Hippocrates (ancient Greek physician) cited, “Let food be the medicine and medicine be the food”. Presently, nutraceuticals may be called the bridge between “food” and “medicine”. Nutraceuticals may be herbal products, regular nutritive products, withdrawn nutrients, vitamins and processed food products (like soups, juices, cereals and beverages) [10].

Treatment of Cancer

After heart disease, cancer is the next leading cause of death. Cancer may occur due to many reasons, such as improper diet, junk foods, smoking and drinking. Treatments for cancer have been developed to cure the disease from ancient times. At present, there are many therapies to treat different types of cancer shown in Table **1**.

Table 1. Therapies that treat different types of cancer.

Name of Therapy	Mechanism of Action	References
Surgery	Removal of the cancerous part of the body.	[12]
Chemotherapy	A cancer cell is damaged or killed with the help of drugs.	[13]
Hormonal therapy	Withdrawal of hormone-secreting gland, *e.g.*, inhibition of adrenal steroid genesis.	[14]
Radiation therapy	X-rays are used for curing cancer.	[15]
Targeted therapy	A specific molecule or cell is targeted for invasion.	[16]
Photodynamic therapy	Photodynamic therapy involves the use of light, oxygen and photosensitizers to cure cancer.	[17]
Stem cell transplant	The affected cells are replaced by healthy cells.	[18]

HEALTH BENEFITS VEGETABLES, SPICES, AND PULSES

As we know, functional foods contain phytoconstituents used in the treatment of various diseases. As reported in the literature, vegetables, spices and pulses have a great potential for prevention and treatment through their anticancer activity. Some potential vegetables that are a remarkable source to treat various cancer types of cancer are listed in Table **2**. Cereals are a good source of peptide-protein and amino acids. Each cereal has its own protein amount. Some peptides are used as nutraceuticals, which exert biological activity and promote health benefits by reducing the risk of various disorders tabulated in Table **3**. From the ancient period, spices are also used as folk medicines. Spices may be used as an anticancer, anti-inflammatory, antioxidant and wound healer [19]. Some common spices and their health benefits are tabulated in Table **4**.

CHAPTER 2

Allium Species: A Remarkable Repertoire of Nutraceuticals with Anti-cancer Properties

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Abstract: Cancer - the name evokes fear and anxiety. Researchers are working tirelessly to bring hope to countless patients by developing prevention and treatment strategies. One approach is dietary modulation - which is documented to reduce the risk of cancer and increase the benefit of anti-cancer therapy. *Allium* species are a part of the daily diet in most parts of the world. Important members of this genus - chives, garlic, onions, and shallots add flavour and nutrition to food. These are prized for their organosulphur compounds and flavonoid content which are responsible for their diverse pharmacological activities. Traditional and scientific literature shows that dietary intake of *Allium* species prevents and aids the treatment of different cancers. In this review, based on an extensive search of available databases, the role of *Allium* species as nutraceuticals for cancer management was examined to ascertain the truth in the popular claims. Preclinical and clinical investigations show that consumption of the *Allium* members as a part of the diet and also the functional components (*e.g*., allicin, diallyl disulphide, diallyl trisulphide, ajoene, S-allyl cysteine, S-allyl mercaptocysteine, tuberoside M, onionin A, fisetin, quercetin, *etc*.) reduce risk of cancer and have significant antitumor activities. These act by varied mechanisms, including inhibition of gene expression, promotion of apoptosis of cancer cells, antiproliferative activity, and anti-oxidant and anti-inflammatory effects. It is emphasised that standardization of *Allium* products, their efficacy, dosage, safety profiles and interactions should be ascertained to corroborate their use. This article highlights the importance of *Allium* species for their prophylactic, therapeutic and immune-boosting ability in cancer management.

Keywords: *Allium* species, Anti-cancer, Dietary components, Flavonoids, Organosulphur compounds.

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Saroj Arora, Tajinder Kaur, Rajendra G. Mehta, Balbir Singh & Sandeep Kaur (Eds.)

INTRODUCTION

The United Nations has put together 'Sustainable Development Goals' for a healthier and happier planet [1, 2]. A major goal amongst these is to ensure good health and well-being for all. Well-being begins with a healthy lifestyle. A healthy lifestyle includes:

- Physical aspects like regular exercise, adequate sleep and diet.
- Mental and emotional positivity and resilience.
- Positive and active social contributions.

When a healthy lifestyle is not maintained, it leads to diseases [3]. Non-communicable Diseases (NCDs), such as diabetes, hypertension, obesity, cardiovascular disorders, osteoporosis and cancers, are the leading cause of death in the world [4]. Fig. (**1**) summarizes the main causes [5] leading to NCDs and the outcomes of possible modification of lifestyle.

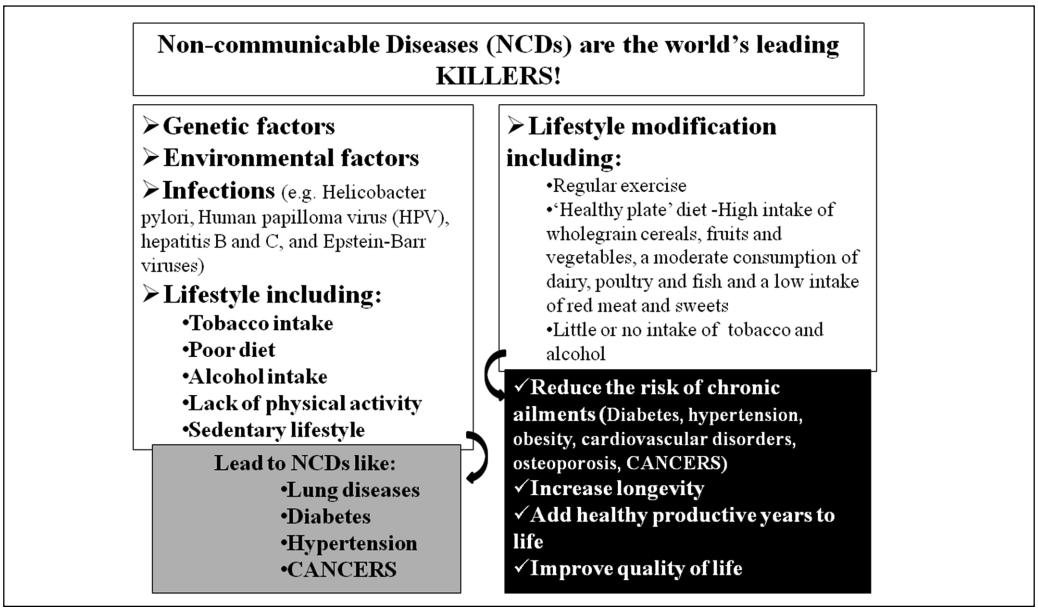

Fig. (1). Impact of different factors and their modification in NCDs. NCDs, especially cancers, are a leading cause of death and also result in immense suffering and economic burden on the patient and the caregivers.

CANCER PREVALENCE

Cancer is a multistage process that is characterised by uncontrolled or abnormal growth of cells which may occur in any tissue. Cancerous cells have the ability to even invade and spread other normal cells and organs [6]. In men, the more

cancer-prone organs are the prostrate, colon and rectum, lung and bronchus, skin and urinary bladder, while in women, breast, uterine corpus, lungs, rectum and colon cancer are more frequent. For children, blood and lymph node cancer constitutes the major clinical cases of cancer [6, 7].

Despite the availability of improved treatments over the past few years, which increased the survival rates of patients [8], cancer is the leading cause of mortality after cardiovascular disorders and is also the reason for 1 in 6 deaths worldwide [9]. Furthermore, each year, the toll of cancer cases and deaths is increasing due to ageing and population growth [10]. It is estimated that cancer cases will double by the end of 2020, and WHO predicted about a 70% increase in the new number of cancer cases by the next 20 years [8]. In low and middle-income countries, about 70% of deaths are due to cancer.

There are numerous risk factors that can trigger abnormal growth of cells, and this includes exposure to noxious chemicals (smoking and alcohol), genetic mutations (changes in cell functions), environmental chemicals (pollution), microorganisms (virus, bacteria) and radiations. Once triggered, it alters the functions of vital genes and disturbs the normal cell cycle leading to abnormal proliferation of cells [6]. Therefore, early diagnosis and treatment are considered essential to reduce mortality among cancer patients.

Management of Cancer

The management of any disorder entails prevention and treatment, along with maintaining the best possible patient quality of life. Cancer researchers are working tirelessly to bring hope to countless patients by developing treatment and prevention strategies.

Management of cancer includes the complete spectrum of care that comprises of:

Prevention, Screening, Diagnosis, Treatment, Palliative care, End of life care.

- Prevention involves a healthy lifestyle (diet and exercise) and routine testing and screening of high-risk groups.
- Diagnosis is the decisive step that helps to determine the occurrence and stage of cancer. Diagnosis involves laboratory tests, imaging scans and pathological examination of tumour samples obtained by performing a biopsy or aspiration. This is critical since the treatment modality depends on this.

CHAPTER 3

Mechanistic Insight into the Chemotherapeutic Potential of Dietary Phytochemicals

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Abstract: Globally, cancer is the main cause of mortality and morbidity. Unfortunately, existing medical procedures are not adequate due to a lack of appropriate therapy, adverse health effects, chemoresistance and disease recurrence. In recent years, epidemiological findings have illustrated the connection between the consumption of several phytochemical-enriched foods and nutrients, and the lower risk of different types of cancer. Natural compounds named 'phytochemicals', commonly found in fruits, vegetables, and whole grains, have shown convincing beneficial biological effects on human well-beings, including curing different types of cancers. Phytochemicals, which are non-nutritive chemicals present in plants, have come up as modulators of essential cellular signaling pathways exerting proven anti-cancer benefits. Dietary phytochemicals have received major interest in chemoprevention as they are thought to be safe for human use. Chemo-preventive agents restrain the growth of cancer either by impeding DNA damage, which contributes to malignancy or by preventing or restricting the division of premalignant cells through DNA damage. Phytochemicals may prevent carcinogenesis by contributing to cell cycle arrest, autophagy and apoptosis. The bioactive compounds have been reported to reverse adverse epigenetic control, including modifying DNA methylation and histone alteration, modulating the expression of miRNA, inhibiting phase I enzymes, and activation of phase II enzymes, scavenging DNA reactive agents, preventing the excessive proliferation of early, preneoplastic lesions, and suppress other properties of the cancer cells. These have all been a part of indirect yet successful and innovative approaches to cancer treatment utilizing phytochemicals.

Keywords: Apoptosis, Cancer, Carcinogenesis, Chemoprevention, Dietary phytochemicals.

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Saroj Arora, Tajinder Kaur, Rajendra G. Mehta, Balbir Singh & Sandeep Kaur (Eds.)

INTRODUCTION

Cancer is the primary reason for mortality in developing as well as developed countries and creates immense pressure on societies at the academic, financial, and political levels [1]. Cancer is classified as a multi-phase disease that can be divided into different stages, *viz.* initiation, promotion, conversion, progression, invasion and metastasis. Many of the chemotherapy drugs target advanced-stage which has some limitations like adverse side effects, quality and single-target mechanisms [2]. Thus, there is an urgent need to quest for new and better therapeutic agents with enhanced cancer therapy potential. Chemoprevention is one such strategy that uses synthetic, natural, or biological agents to prevent, suppress or reverse the initial step of carcinogenesis or to avoid the invasive potential of premalignant cells [3]. With growing awareness of chemoprevention, genetics, and achievements in breast, prostate, and colon cancer prevention, the interest in chemoprevention has increased considerably [4]. At the molecular level, chemoprevention has been characterized by the modification of various pathways that play a key role in the three basic steps of carcinogenesis, *i.e.*, initiation, promotion, and development [5]. Clinically, chemoprevention has also been classified as primary, secondary, and tertiary. Primary chemoprevention is effective for the general population without cancer, and also for populations at high risk of developing cancer throughout their lifetime. Secondary chemoprevention is designed for its use in patients with pre-malignant lesions that can lead to invasive carcinoma. Typically, primary and secondary chemoprevention was known as primary chemoprevention. Examples of the principal chemo-preventive agents are phytochemicals and non-steroidal anti-inflammatory dietary drugs. On the other hand, tertiary chemoprevention is intended to avoid the recurrence of cancer [6].

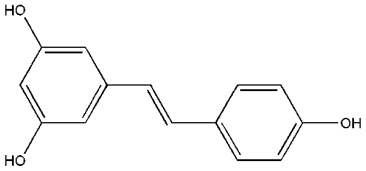
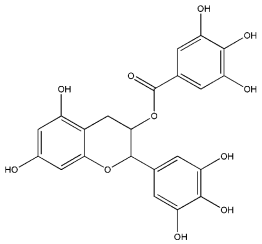
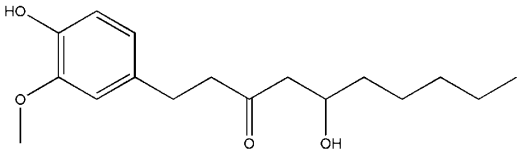
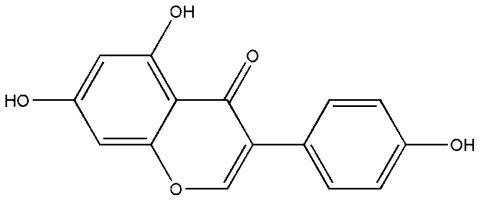
Chemoprevention by dietary phytochemicals has emerged as an effective anticancer therapy as it reduces costs and prevents adverse side effects. Moreover, different phytochemicals may play an ameliorative role at different or multiple stages during cancer development [7]. Phytochemicals are non-nutritive secondary plant compounds with disease-preventive and health-promoting activities that are typically found in grains, fruits, spices, vegetables, herbs, and other plant foods. The health-promoting effects of dietary phytochemicals have been conventionally unveiled by several epidemiological studies, preclinical and clinical research evidence which previously found a clear association between the consumption of vegetables and fruits and a reduction in the risk of developing various diseases, including different types of cancer. Recent studies have led to the discovery of particular dietary phytochemicals with anticancer properties [8, 9]. Within this chapter, we will discuss the role of certain chemo-preventive agents from dietary sources examined through some epidemiological and

laboratory data about their impact on cancer cell lines and animal studies dealing with the treatment of cancer.

NATURAL PHYTOCHEMICALS FOR CANCER CHEMOPREVENTION

Phytochemicals are bioactive substances present in many herbs, spices, fruits, vegetables, and grains. Many positive health benefits are due to phytochemicals. A large proportion of phytochemicals have been recognized, but many of them with potential beneficial effects are still undiscovered and need explanation [10]. Many natural compounds have been identified as potential chemo-preventive agents (Table **1**). Some of these phytochemicals with chemo-preventive potential have been discussed below:

Table 1. List of phytochemicals used as chemo-preventive agents.

S.No.	Phytochemical	Source	Structure
1.	Resveratrol	 Red Grapes	
2.	Epigallocatechin gallate (EGCG)	 Green Tea	
3.	Gingerol	 Ginger	
4.	Genistein	 *Genistatinctoria*	

CHAPTER 4

Complementary and Alternative Strategies for Cancer Prevention and Therapy

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Abstract: Alternative and complementary therapies have been widely used for the treatment of cancer throughout the world. The term 'Complementary and Alternative' (CAM) was used by the American Cancer Society and the Union International Centre le Cancer (UICC). Complementary and alternative medicines mean anything which is not conventional; the reasons to adopt these therapies are that it makes use of the procedures used in adjunct to mainstream therapy in order to improve the quality of life. Several evidences were put on trial that support the value of hypnosis for cancer pain and nausea, mind-body therapies, relaxation therapy, massage for anxiety, acupuncture, homeopathy, Ayurveda, chiropractic medicine and osteopathy. The use of unconventional agents, pharmacological and biological agents, diet and nutrition and herbal therapies are amongst some of the most recent advances in alternative cancer therapies. This article reviews the various popular cancer therapies commonly practiced in India and abroad and reveals the scenario of various complementary and alternative cancer therapies.

Keywords: Acupuncture, Anxiety, Ayurveda, Homeopathy, Hypnosis, Massage, Osteopathy.

INTRODUCTION

Various unauthenticated or questionable methods are used for the treatment of cancer patients throughout the globe, which compromise the diagnostic tests, or certain preventive measures, the scientific basis of which has not been proven yet [1]. The term CAM stands for Complementary and Alternative Medicine, and is used by the American Cancer Society *vis a vis* Union International Centre Le Cancer (UICC). The terminologies define complementary and alternative medi-

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cine as any treatment which is not conventional [2, 3]. This term is quite beneficial as it provides an opportunity to distinguish between the two. Alternative therapies being biologically active are encouraged for use rather than using conventional methods. On the other hand, complementary therapies are used in addition to mainstream therapy in order to manage and improve the standards of life of humans [4]. US cancer Centers has changed CAM acronym to CIM, which means Complementary and Integrative Medicine [5].

Despite having quite a long history in ancient Chinese and Ayurveda, CAM has recently been on the trend. Among the developed countries, CAM is used to 42.1% in USA, 48.2% in Australia and 70.4% in Canada, while in developing countries, the percentages touch 71% in Chile, 70% in China, and 80% in African countries [6]. Henceforth, more scientific evidence is required to support the better use of CAM. National Center for Complementary and Alternative Medicine was founded under NIH in 1998 and investigated the efficiency of CAM practices, which had some scientific evidence [7]. Under this centre, CAM methods were classified under five different headings *viz*., mental and physical practices, alternative medicine practices, biological treatments, manipulative and physical practices and energy therapies [7]. Cancer is a very common disease for which CAM therapy is commonly practiced. GLOBOCAN provided the data in 2012 in collaboration with International Agency for Research on Cancer (IARC), according to which there exist 14.1 million new cases of cancer-causing 8.2 million deaths. The cancer incidence, however, depends upon the improvements that have occurred in the early diagnosis by using conventional therapies like chemotherapy, radiotherapy, surgical methods, *etc*., ultimately leading to extended life expectancy rates. Since the majority of people nowadays want to increase the rate of survival without facing the side effects of the treatment hence an increase of 30-50% has been observed in the use of Complementary and Alternative methods of therapy [8 - 12].

REASONS FOR GROWING INTEREST IN ALTERNATIVE THERAPY FOR CANCER

One of the major reasons for the growing interest of people in alternative therapies is the widespread concern regarding the inability of medicines to treat cancer. People are highly concerned about the growing rate of incidence of cancer and the absence of real treatment. Another reason is the adverse effects of conventional cancer treatment therapies. Thus, their growing dissatisfaction with the technology and modern scientific methods created a desire to search the alternative methods of treatment [13]. Insensitive complaints are received by patients from suburban hospitals to the topmost cancer research institutes regar-

ding the side effects of chemotherapy. They are even told that these are much more likely to happen after chemotherapy.

Thus patients automatically withdraw their interest in mainstream medicine and start bending towards the use of complementary therapies that are more health-conscious and provide emotional satisfaction in addition to communicative relationships [13]. In a survey, it was observed that people practicing CAM therapies were emotionally stronger even though the condition of cancer remains unaffected [14].

COMPLEMENTARY THERAPIES FOR CANCER

A large proportion of cancer patients use complementary cancer therapies to relieve stress and improve their standard of life by relaxing their muscles. Muscular relaxation, a popular technique, involves contraction and relaxation of the muscles. One other is hypnosis, which means the induction of a deeply relaxing state with an increasing suspension of critical faculties [4]. Also called the hypnotic trance, this state induces behavioral changes in the patient that act as a driving force to provide relief. Also, in some access, visualization is involved in which a relaxed state is followed by the production of a visual which is pleasant, thus enhancing the feeling of relaxation. These techniques are, however, not effective against nausea which is caused during bone marrow transplantation [15].

Acupuncture is known to cause a reduction in nausea and vomiting. By the stimulation of P6, which is a point found proximal to the wrist alone or in combination with ST 36 stimulation (present in the lower leg), standard antiemetic meditative procedures can be applied [16]. Also, acupuncture in cancer patients is responsible for causing palliation of chronic pain. Previous reports have been put on record that suggests that acupuncture can provide relief better than conventional treatment methods [17, 18]. Also, therapeutic massages that involve the manipulation of soft tissue are known to provide relief from muscular aches and body pain. Lesser reports have been documented that provide evidences regarding the role of massages in the treatment of pain in cancer patients [19, 20].

BODY MIND RELATED THERAPY

This therapy involves focusing on the various interactions between the body and mind to minimize the symptoms and promote health. Some of the common therapies are hypnotherapy, yoga, meditation and music therapy. The ultimate motive of such therapy is to minimize the effects of anger, fear, depression, anxiety and pain in the patient, thereby increasing the feeling of spiritual and physical well-being and helping to improve the standard of life. Studies have revealed that such techniques reduce anxiety and stress in conjunction with other

CHAPTER 5

Current Trends in Target-Specific Delivery of Phytomedicine: A Possible Strategy for Cancer Treatment

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Abstract: Cancer is a leading source of illness and mortality around the world. Despite the fact that primary cancer treatment has considerably reduced cancer mortality, the survival rate remains low due to tumour metastasis, a variety of adverse medication responses, and drug resistance. Alternative medicines, particularly herbal medications, have piqued the interest of scientists due to their high efficacy and low toxicity. However, their limited water solubility, low stability, poor absorption, and quick metabolism limit their therapeutic usefulness. Due to these constraints, the focus of phytocancer therapy has switched to tailored drug delivery systems. Nanomedicine, which involves using nanoparticles as drug delivery vehicles to boost the therapeutic benefits of phytochemicals, has a wide range of uses in cancer treatment. Many challenges in drug delivery to cancer cells can be overcome by using nanoparticulate drug carriers, including improved solubility and bioavailability, drug targeting, reducing adverse effects in non-target organs, high efficacy, low drug resistance, and high drug concentration at the tumour site. The present review entails the most recent advancements in anticancer phytodrug delivery employing nanocarrier-based technologies.

Keywords: Anti-cancer, Cytotoxicity, Drug delivery system, Nanotechnology, Phytochemicals.

INTRODUCTION

Cancer is one of the most serious challenges to humanity, and it is the world's second biggest cause of death. It is responsible for 7.6 million deaths, with the

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Saroj Arora, Tajinder Kaur, Rajendra G. Mehta, Balbir Singh & Sandeep Kaur (Eds.)

number expected to climb to almost 13.1 million by 2030. Surgery, radiation, chemotherapy and a combination of these treatments are the mainstays of traditional treatment. Chemotherapeutic drugs destroy both normal and cancer cells by targeting fast-dividing cells, such as hair follicles and epithelial cells in the digestive tract. They also acquire resistance to tumour cells with extended use. Following treatment, patients frequently experience relapse and malignant cell metastases [1 - 3]. As a result, it's critical to use natural and safe drugs that limit tumour growth and can target many biological pathways in cancer cells while causing no damage in normal cells. Herbal therapy has recently received a lot of interest as a treatment for a variety of ailments. Phytochemicals, a family of bioactive molecules found in vegetables, fruits, grains, and other plant parts, have been shown to be effective against such a deadly disease. Several bioactive phytochemicals, including camptothecins, berberine, catechins, celastrol, curcumin, quercetin, and resveratrol, have the anticancer potential [4]. Regardless of these phytoconstituents' biological merits, their use in the therapeutic area has a long way to go. Low water solubility, poor bioavailability and poor targeting are among the issues that contribute to their reduced use. For current treatment regimens to increase tumour cell activity while decreasing harm to normal cells, drug targeting is essential. Many studies have shown that nanotechnology-based delivery of phytoconstituents can easily solve these issues [5 - 7].

Nanomedicines' enhanced permeability and retention (EPR) effect is a powerful tumour targeting method. The majority of solid tumours have inadequate lymphatic drainage and blood vessel architectural defects. The EPR effect allowed macromolecules and nanomedicines to ‘leak' from blood arteries around a tumour, and inefficient lymphatic drainage in tumours allowed them to concentrate in the vicinity of the cancer cell, reducing clearance from the targeted tissue. EPR effect does not take place in normal tissues. The size and surface qualities of nanomedicine are the essential parameters that influence the EPR. Nanomedicine with a molecular weight of more than 40 kDa (macromolecules) and a particle size range of 1-100nm can accumulate in malignant cells via EPR. To allow enough time for medication distribution via the EPR effect, a long circulation time is required. Low molecular weight phytoconstituents have a wide distribution in normal organs and tissues [8].

Multidrug resistance (MDR) is another key issue that contributes to the failure of phytochemical therapy in cancer treatment. Overexpression of proteins from the ATP binding cassette (ABC) transporter superfamily causes MDR. These MDR proteins, particularly P-glycoprotein (Pgp), are responsible for drug efflux that is energy dependent, resulting in lower intracellular accumulation of chemotherapeutic medicines as doses are increased. Nanocarriers for phytochemical delivery are one of the novel strategies for overcoming MDR.

Surface modification of nanomedicines alters the biophysical interactions of nanomedicines with cancer cell membrane lipids, enhancing phytomedicine distribution to target tissues and thereby controlling drug resistance [9].

As a result, nanotechnology can be used to improve tumour diagnostics, medication delivery to tumour cells, and molecular targeted cancer therapy, resulting in increased efficacy and patient compliance. The purpose of this review is to summarise the use of several drug delivery systems to deliver promising anticancer phytochemicals.

LIPOSOMES

Liposomes are nanosized phospholipid molecules that form spontaneously when phospholipids are dispersed in an aqueous environment. Liposomes are vesicular drug delivery systems that can encapsulate both hydrophilic and lipophilic medicines and are biocompatible and biodegradable (Fig. **1**). Liposomes have a lot of potential for delivering different compounds for cancer treatment. As liposomes are made up of lipids, they are quickly absorbed in the liver and taken up by macrophages, reducing their potency. Surface modification with ligands such as monosialoganglioside, PEG, polyvinylpyrrolidone polyacrylamide lipids, and glucuronic acid lipids is used to avoid this by physically adsorbing on the vesicle's surface; this is called Stealth liposomes. Another type of liposome is non-stealth liposomes, which are made at a high phase transition temperature. Although these phospholipids have a high percentage of liver uptake, they nevertheless aid in extending circulation time and accumulation within cancer cells [10 - 12].

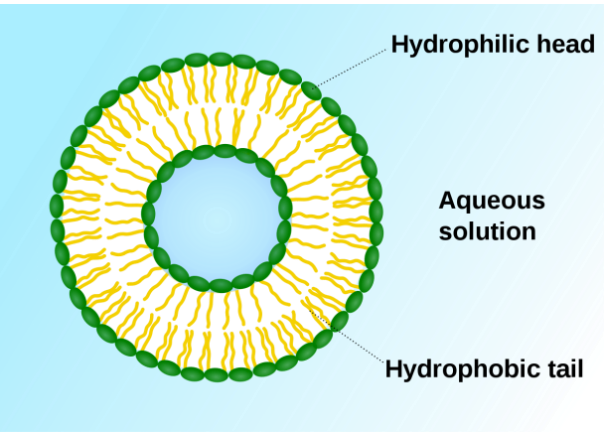

Fig. (1). Structure of unilamellar liposomes.

CHAPTER 6

Antioxidants and Oxidative Stress as Foe and Friends in Prevention of Cancer

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Abstract: Cancer has become a major public health problem and is one of the leading causes of death among humans worldwide. It is characterized by the abnormal proliferation of cells due to failed normal regulatory mechanisms. Oxidative stress plays a crucial role in the pathology of many cancers and is characterized by an imbalance between the production and removal of reactive oxygen species (ROS). Under normal physiological conditions, the intracellular levels of ROS are steadily maintained to prevent cell damage, and detoxification of ROS is facilitated by various non-enzymatic and enzymatic antioxidants. These antioxidants have a widespread application in the prevention of cancer, as many endogenous and exogenous antioxidants can prevent and repair damage caused by disrupted redox status of cells during carcinogenesis. Our body can produce some of the antioxidants, but to obtain the rest of the antioxidants, it relies on external sources, primarily the diet of an individual. Also, there are certain health issues reported with the long-term usage of synthetic antioxidants. Therefore, nowadays, many nutritionists and dieticians suggest consuming food and natural products that are either rich sources of antioxidants or are supplemented with various nature-based antioxidants. This chapter seeks to explain the role of ROS in oncogenesis, understand the dynamics between oxidative damage and the antioxidants, types of antioxidants, natural sources of antioxidants, mode of action of antioxidants and the role of antioxidants in cancer prevention and treatment along with their disputable effects in cancer therapy.

Keywords: Antioxidants, Cancer, Oncogenesis, Oxidative stress, Reactive oxygen species (ROS).

INTRODUCTION

It is needless to mention cancer as a fatal disease, characterized by the uncontrolled proliferation of cells and eventually their transformation into malig-

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Saroj Arora, Tajinder Kaur, Rajendra G. Mehta, Balbir Singh & Sandeep Kaur (Eds.)

nant cells. It is one of the leading causes of death worldwide, and keeping in view its distressing spread, it can amplify the mortality rate if not controlled [1]. Damage caused to DNA, and other biomolecules by ROS is the leading cause of the onset and progression of cancer. ROS are the by-product of the normal metabolism of the cell and usually increase during inflammation and on exposure to intrinsic factors such as nitric oxide pollutants, smoke, certain drugs and radiations. Elevated levels of ROS inside the cell can lead to the oxidation of lipids and proteins, induce cancer-causing mutations and alteration of cell signalling pathways leading to cancer [2 - 4]. The role of ROS in cancer is supported by experimental studies showing that dietary antioxidants such as vitamin E, vitamin C, β-carotene, selenium and certain other phytochemicals, as well as some endogenously generated antioxidants like glutathione, trap or neutralize ROS, thereby acting as cancer thwarting agents [4, 5]. Antioxidants, also known as "free radical scavengers," are chemical compounds that prevent free radicals from causing damage. They are well known to interact with and neutralize free radicals. Some of the antioxidants are produced within the body to neutralize free radicals and are therefore called endogenous antioxidants. They include enzymes such as superoxide dismutase, glutathione peroxidase and catalase, and some non-enzymatic antioxidants such as glutathione, uric acid, bilirubin and metal chelating proteins. However, in order to obtain the rest of the antioxidants, the body relies on outside sources, primarily the diet of the individual. Such antioxidants obtained from external sources are called exogenous antioxidants or dietary antioxidants. Grains, fruits and vegetables are high in antioxidants and therefore are a rich source of dietary antioxidants. However, many of the dietary antioxidants are also available as dietary supplements [6, 7]. Keeping in view the ROS scavenging capabilities of antioxidants, many nature-based products having antioxidant activities have been identified to be used as potent anti-carcinogenic agents in cancer prevention and treatment in addition to conventional cancer treatment options, such as chemotherapy, surgery and radiotherapy [8].

OXIDATIVE STRESS AND CANCER

In the course of evolution on planet earth, organisms have developed the ability to utilize molecular oxygen as a terminal oxidant [9]. Aerobic metabolism includes the use of oxygen for the generation of chemical energy useful for life in the form of ATP [10]. Despite the various advantages of O_2-dependent metabolic processes and aerobic respiration, the generation of ROS as by-products of O_2-dependent processes can potentially cause damage to cellular macromolecules like proteins, lipids and nucleic acids [11]. In order to counter the damage caused by these ROS, living organisms have developed an antioxidant defense system that comprises various enzymatic and non-enzymatic molecules called antioxidants.

As a consequence of an imbalance between the ROS production and their sequestration by the antioxidants, the redox status of the cell can get altered, thereby resulting in an increase of overall intracellular ROS levels or oxidative stress [12]. If this oxidative stress is mild, the antioxidant defense system is upregulated to restore normalcy inside the cell. But if the oxidative stress is severe, it may lead to many deleterious processes inside the cell [10]. Some specific diseases mediated by ROS-generated stress include Alzheimer's disease [13], Parkinson's disease [14], cancer [15], Down's syndrome [16], Atherosclerosis [17], aging [18] and ischemic reperfusion injury in various tissues including brain, kidney, heart, gastrointestinal tract and liver [19]. Cancer cells are characterized by a large amount of ROS production and oxidative stress along with disrupted antioxidant activity than other non-neoplastic cells [20]. ROS-mediated DNA damage promotes tumor initiation and progression as damaged DNA leads to increased genetic instability that may further cause activation of oncogenes or inhibition of tumor suppressor genes, thus promoting the malignant potential of tumor cells [21]. Further these mutations tend to accumulate with age [22].

FREE RADICALS AND ROS

Chemical species with an unpaired electron in the outer electronic shell are called free radicals. They are capable of independent existence and are highly unstable moieties due to unpaired electron that makes them reactive towards other molecules [23, 24]. Reactive species is a general term encompassing both free radicals and non- radical derivatives called oxidants. Some of the commonly encountered free radicals and oxidants are given in Table **1** [25, 26].

Table 1. List of the commonly encountered free radicals and oxidants.

FREE RADICALS	OXIDANTS
Superoxide anion radical	Singlet oxygen
Hydroxyl radical	Ozone
Peroxyl radical	Hypochlorite
Lipid radical	Hydrogen peroxide
Hydroperoxyl radical	Peroxynitrous acid
Lipid alkoxyl radical	Nitrous acid
Lipid peroxyl	Nitrous oxide
Protein radical	-
Thiyl radical	-
Nitrosyl cation	-

CHAPTER 7

Efficacy of Chemopreventive Agents in Steroid Hormone Dependent Mouse Mammary Organ Culture (MMOC) Model: A Comprehensive Review

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Abstract: Currently, Breast cancer is the leading cause of cancer mortality in women in U.S. and accounts for a high proportion of new cancer cases in this population. Cancer chemoprevention is a new approach in cancer prevention, in which chemical agents derived from the natural and synthetic source are used in nontoxic concentrations to prevent cancer in normal and/or high-risk populations. To date, numerous cancer preventive agents derived from natural products have been evaluated for their cancer chemopreventive potential. The cancer chemopreventive agents have been isolated from natural sources and/or synthesized and evaluated for their efficacy in a variety of biological assays. As a part of our cancer chemopreventive program spanning more than three decades, we established and utilized a mouse mammary gland organ culture model (MMOC) as a preliminary screening bioassay. This assay was used to evaluate natural-based compounds or their synthetic analogs. Mammary glands respond to growth-promoting hormones, and the physiological differentiation can be reproduced in MMOC. The estrogen and progesterone-dependent mammary ductal lesions (MDL) can be induced in response to a 24-hour exposure to DMBA in MMOC. In order to evaluate the efficacy, we analyze the suppression in the incidence and multiplicity of the lesions. Suppression of the incidence and multiplicity of these lesions by a possible chemopreventive agent can serve as a tool to evaluate the efficacy of potential experimental agents. Using this approach, we have evaluated more than seventy natural product-derived and synthetic chemopreventive agents as a part of the National Cancer Institute-supported projects. It may be worth mentioning that a substantial number of these chemopreventive agents having significant activity in this assay also showed encouraging results *in vivo* experimental studies. This bioassay not only provided a valuable tool for screening cancer chemopreventive agents for breast cancer prevention but also helped in understanding molecular mechanism(s) of action. In this comprehensive review, we provide a complete list of chemopreventive agents

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Saroj Arora, Tajinder Kaur, Rajendra G. Mehta, Balbir Singh & Sandeep Kaur (Eds.)

evaluated for efficacy against the development of mammary ductal lesions (MDL) in MMOC, along with the recent developments in *in vivo* mammary carcinogenesis.

Keywords: Cancer chemopreventive agents, Evaluation, Mouse mammary organ culture (MMOC), Mammary ductal lesions (MDL).

INTRODUCTION

Cancer is a highly complex and multi-factorial disease that can affect all multicellular organisms. After cardiovascular disease, it is the leading cause of death amongst the global population, responsible for more than 7 million deaths in a year [1, 2]. Cancer, in fact, is a term used for a group of diseases that have the capacity to invade surrounding normal tissue, metastasize (spread to distant sites) and kill the host. Cancer, a result of excessive cell proliferation, is caused by damage to the regulatory genes resulting from diverse kinds of exposures. These exposures may occur through various routes of uptake and may involve chemical compounds that may be involved in the initiation or promoting (with or without bio-activation), irradiation and viruses. Involving three stages initiation (mutation of the DNA), promotion (increased rate of cell growth) and progression (formation of malignant tumors), cancer in fact, is a class of disease in which the structure and function of the genetic information coded in the DNA have changed.

Breast cancer, the most common worldwide neoplasia in women, may be caused because of genetic, environmental, and endocrinal factors in addition to lifestyle factors. The estimates from the National Cancer Institute state that with the current rate, women born now have an average risk of 12.7 percent (often expressed as “1 in 8”) of being diagnosed with breast cancer at some time in their lives [3]. In spite of the tremendous progress made in the treatment and therapeutic strategies, the incidence, morbidity and mortality of cancer remain a major global challenge. In the ongoing efforts to address the challenges of cancer, the utilization of chemopreventive agents to target multiple pathways has evolved as a promising strategy for protection against various types of cancer. Cancer chemoprevention is defined as the use of natural, synthetic, or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer. Unlike chemotherapy therapy, cancer chemoprevention focuses on the prevention or treating premalignant lesions.

The discovery of botanical natural products that act as cancer chemopreventive agents involves bioassay-guided fractionation of the plant product as the preliminary step. A disease-oriented approach to screening potential chemopreventive agents is important, considering the specificity and diversity of

tumors. Most recently, the major focus in cancer chemoprevention is developing translational/mechanistic studies to develop novel chemopreventive agents and identify surrogate endpoints. Over the period, the elucidation of the molecular and biochemical mechanism of carcinogenesis has allowed bioassays to be developed that screen for agents that are effective at specific target sites.

The process of evaluation of the efficacy of chemopreventive agents is a multistep process, much like the oncology therapeutics; however, the clinical development of cancer chemopreventive agents is much more complex. Protection from the carcinogen (from an environment) by an intervention agent might enhance a physiological process protecting humans against preneoplastic cell progression or neoplastic growth [4, 5]. Cancer chemopreventive agents may intervene by preventing the formation of carcinogens *via* inhibiting metabolic activation of carcinogens or by acting as a blocking agent by preventing the carcinogens from binding to critical sites such as DNA. The agent may also be involved in hindering the development of tumors after exposure to a carcinogen by preventing tumor cell proliferation, induction of apoptosis or inducing differentiation. During its relatively brief history, cancer chemoprevention has established itself as one of the most promising areas of cancer research. In recent years, cancer prevention by natural products has received considerable attention. Cancer chemoprevention and attendant clinical studies have increased impressively, as evidenced by the large volume of literature it has generated. Our group has contributed by summarizing important findings in numerous reports [6 - 9]. Over the last few years, the focus of cancer chemopreventive research has shifted to the molecular level and biochemical mechanisms of the carcinogenesis process have been elucidated [10, 11].

The first part of screening involves *in vitro* evaluation of potential cancer chemopreventive agents, which includes measurements of agents' antioxidant activity, induction of phase II metabolizing enzyme, effect on cellular proliferation and apoptotic control pathways [12, 13]. Diverse cell lines have been developed based on the different mechanisms of action [14, 15]. The *in vitro* tests, in general, provide a measure of the efficacy of the compounds in blocking the transformation of the cells and the blocking of the growth of transformed cells. It may be worth mentioning that there exists no universal relationship between the activities of the compounds for different sites. Certain retinoids can be very much efficacious in one cell line but might be inefficient in other systems. The compound, which shows promising activity graduates to the next level of *in vivo* efficacy evaluation, where the rodent model is utilized for target organ carcinogenesis. Animal models of chemical-induced mammary carcinogenesis with 7, 12-dimethylbenz[a]anthracene and N-methyl-N-nitrosourea have been useful in the study of biology, treatment and prevention of breast cancer [16, 17].

CHAPTER 8

Molecular Mechanisms of Flavonoids Mediated Therapy and Chemoprevention of Cancer

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Abstract: Flavonoids derived from daily dietary source and plant products play a crucial role in the prevention and treatment of various degenerative diseases and cancer. Flavonoids are further subdivided into subclasses such as flavones, flavan-3-ols, flavonols, flavanones, isoflavones and anthocyanidins. There has been a resurgence in the research on flavonoids due to enhancement in the evidence that proves the health benefits of flavonoids. Several preclinical and epidemiological studies revealed that dietary intake of flavonoids may be found helpful in the reduction of risk of tumors like colon, breast, lung, pancreas and prostate. It also acts on the reactive oxygen species, and cellular signal transduction pathways associated with cellular proliferation, angiogenesis and apoptosis. Flavonoids are non-toxic in nature, so intensively studied the broad, vast aspect of their efficacy in biological activities that in turn promotes health benefits and also added to its availability in abundance in our daily diets, for instance, fruits, green leaves, tea, red wine and vegetables. Overall, the exciting data obtained so far elicit that dietary flavonoids have been considered a beneficial cancer preventive approach. This chapter unravels the molecular mechanisms involved in potential cancer preventive efficacy accomplished by the novel biological approach of flavonoids.

Keywords: Abiotic stress, Anti-cancer, Anti-inflammation, Anti-tumor, Biotic stress, Chemoprevention, Saponins, Secondary metabolites.

INTRODUCTION

Flavonoids are synthesized by plants as secondary metabolites found to be polyphenolic compounds [1]. The basic structure of flavonoids is a 15-carbon

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skeleton, with two benzene rings which are connected by a 3-carbon linking chain forming a basic benzo-pyrone C6-C3-C6 system. There are more than 9000 flavonoids grouped into various classes and subclasses. They are broadly classified into six major classes isoflavonoids, flavanones, flavanols, flavonols, flavones and anthocyanidins [2, 3]. A large number of flavonoids is due to the substitution of their basic structure with multiple hydroxyl, methoxyl, and O-glycoside groups. Flavonoids are one of the main components of the human diet, as they are present abundantly in fruits and vegetables [4]. It has been studied that the intake of fruits and vegetables can reduce the risk of cancer by 20%. So the isolation of the compounds having cancer-preventive characteristics from plants became a much-focused area, and now this is confirmed by various *in vitro* and *in vivo* studies that a major class of flavonoids possesses anticancerous properties [5].

The cancer preventive properties of flavonoids are due to their interaction with cellular targets. They act by modulating ROS, scavenging enzyme activities, arresting the cell cycle, induction of apoptosis, autophagy, and suppressing cancer cell proliferation and invasiveness [6 - 8]. The mechanisms with which flavonoids exert their chemopreventive properties include inhibition of phase I metabolizing enzymes like P450 isozymes (CYP1A1 and CYP1A2) involved in activating procarcinogens [9, 10], phase II metabolizing enzymes (*e.g.*, glutathione-S-transferase (GST), quinone reductase, and UDP-glucuronosyl transferase) are induced by flavonoids as a result of which carcinogens are detoxified & eliminated from the body [9, 11], suppressing xanthine oxidase [12], cyclooxygenase-2 (COX) [13] and induced tumor cell proliferation [9], epidermal growth factor receptor/mitogen-activated protein kinase (EGFR/MAPK), phosphatidylinositide 3-kinases (PI3K), protein kinase B (Akt), as well as nuclear factor kappa-light-chain enhancer of B-cells NF-kB activity, is restrained by flavinoids to suppress proliferation of cancerous cells [1, 2, 8].

Studies revealed that there are large no. of flavonoids that are active against different types of cancers like Breast cancer [14], Stomach and Colorectal Cancer [15], Lung Cancer [16], Prostate Cancer [9], *etc*. There are plenteous data that tells us about the antineoplastic properties of various substituents of Flavonoids. Some of the examples are i) Quercetin (flavonol) is known for its activity on human breast cancer cell line MCF-7 and the results reveal that it inhibits MCF-7 cells activity by two mechanisms that are both by arresting MCF-7 in G2/M phase of the cell cycle and by inducing apoptosis [17]. ii) Five flavonoids from the leaves of the chinese medicinal herb *carya cathayensis* were extracted, which are Cardamonin, Pinostrobin, Chalcone, Wogonin, Chrysin and Pinocembrin. These flavonoids, when studied for their effect on vascular endothelial growth factor (VEGF) induced angiogenesis and VEGF induced proliferation and migration in

human umbilical vein endothelial cells (HUVECs), the results have shown that Cardamonin is very effective against VEGF-induced proliferation and Cardamonin, Pinocembrin, Chrysin suppress VEGF-induced HUVEC proliferation and migration [18]. iii) Milk thistle (*Silybum marinum*) seeds contain a flavonolignan called Silibinin which is found to be active against human Prostate Cancer (PCA) and that too both in androgen-dependent and independent PCA cells. Silibinin performs its function by down-regulating EGFR-Erk1/2 activation, TGF expression and secretion in LNCaP and DU145 cell lines and thereby represses their growth [9, 19, 20]. iv) Naringenin (Flavanones) leads to the inhibition of proliferation and migrations in placental choriocarcinoma cells, confirming its anticancerous activity. Naringenin is found to work by inducing ROS generation and ROS-mediated apoptosis in JAR and JEG-3 cell lines by regulating ERK1/2 MAPK and P38 MAPK signal transduction pathways [1, 21]. v) Genistein, Daidzein and Glycitein are important isoflavones that are considered as anticarcinogenic as they cause inhibition of PTK (protein tyrosine kinase) [22], DNA topoisomerase II [23], antiproliferation, and cell cycle arrest, *etc.* [24]. and so on.

Therefore the present chapter will highlight the mechanistic approach of the anticancer properties like antiproliferative, anti-inflammatory, apoptosis-inducing, anti-invasive and anti-metastasis of the subclasses of flavonoids.

Anticancer Properties of Flavonols and Flavones

Antiproliferation can be accomplished by inhibition of tumor-promoting prooxidant agents, usually reactive oxygen species, a growth-promoting oxidant that serves as the primary catalyst for tumour progression and promotion to the initiation point, *i.e*., metabolic carcinogen to mutagens. Tumor promoters, like lipoxygenases and arachidonate metabolising enzymes, trigger or cause prooxidants by cyclooxygenases that are phorbol esters, and flavonoids are generally successful in inhibiting xanthine oxidase [25]. Suppression or retardation of cell hyperproliferation is linked with the control of cancer. Dietary flavonoids are well-documented to act as specific inhibitors of cell growth. In fact, one of their biological properties in plants is to provide phytoalexins with resistance to fungal or bacterial growth [26]. While most flavonoids seem non-toxic to humans, certain forms of cultured human cancer cell lines were shown to inhibit proliferation. Flavonol, like Quercitin (Qu), blocks tumor cell proliferation, in a concentration-dependent way. Though Qu's initial anti-proliferative activity is roughly demonstrated at small concentration levels [27], Qu inhibits tumor formation by modulating PI3K, and Her2 [27, 28].

CHAPTER 9

Protective and Therapeutic Effects of Plant Saponins

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Abstract: Saponins are a large family of biologically active amphipathic glycosides of triterpenoids and steroids. These high molecular weight glycosides consist of an oligosaccharide moiety linked with an aglycone, also known as sapogenin (triterpenoid or steroid). Therefore, structurally saponins are classified into two categories, *i.e.*, triterpenoid saponins and steroidal saponins. They have foaming capacity. They are produced mainly by plants belonging to classes Magnoliopsida and Liliopsida and marine organisms such as starfish, sponges and sea cucumbers. They are non-essential for basic plant metabolism, however, they are produced as secondary metabolites in plants in the presence of biotic and abiotic stresses. Saponins are found in all parts of the plant, including flower, fruits, stem, leaves, *etc*. Many plants that have medicinal properties or are part of the human diet contain saponins. Their concentration in a plant depends on the type of tissue, physiology, genetic makeup and environment of the concerned plant. They impart a pungent and bitter taste to plants. Various studies across the globe have shown that saponins are chemopreventive, anti-tumor, anti-inflammatory, anti-diabetic and anti-obesity in nature. In this chapter, an account of the role of saponins in the prevention and therapy of different health problems, especially cancer in human beings, is presented. This chapter consists of details about the structure, synthesis, sources and biological activities of saponins found in various plant sources used as food. An attempt is also made to compile results from different studies conducted globally to explain the protective and therapeutic effects of saponins.

Keywords: Abiotic stress, Anti-cancer, Anti-inflammation, Anti-tumor, Biotic stress, Chemoprevention, Saponins, Secondary metabolites.

INTRODUCTION

In modern times, poor dietary and lifestyle habits have led to an increase in the worldwide prevalence of various diseases and disabilities in human beings, such

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Saroj Arora, Tajinder Kaur, Rajendra G. Mehta, Balbir Singh & Sandeep Kaur (Eds.)

as psychological problems, neurological disorders, diabetes, hypertension, obesity, dyslipidemia, hormonal imbalances, cardiovascular diseases, cancer, *etc*. [1 - 7]. Plant-based foods are highly recommended by nutritionists because if incorporated in diet, they help in achieving good health and decrease the risk of developing a disease as they have high nutritive value, abundant in dietary fiber, minerals, vitamins and contain various phytochemicals and bioactive compounds with anti-oxidative properties [3, 8]. In different parts of the world, such as, USA, Australia, Japan and Europe, natural functional foods with high nutritional value are marketed for better health of the human population as these foods are considered to enhance immunity, prevent diseases, help in better digestion and prevent ageing [9].

Cancer is one of the major causes of human mortality across the globe [10]. Research studies carried out suggest that poor diet has a huge contribution to an elevated risk of occurrence of cancer and other health problems in humans [1, 11, 12]. Many studies have proved that plant based nutritious diet contains various phytochemicals such as phenolic acids, pigments, tannins, flavonoids, peptides, polysaccharides, terpenoids and saponins may help in the prevention of cancer and other health problems [3, 9, 12 - 17]. Saponins are bioactive compounds that are present in many plants and marine organisms and have a role in the prevention and therapy of various cancer and non-cancerous health problems in human beings. This chapter is a comprehensive review of literature focusing on different aspects of plant-based saponins, including their sources, structural composition, biosynthesis and biological activities in detail.

SAPONINS: STRUCTURE, TYPES, SOURCES AND PROPERTIES

Saponins are a group of high molecular weight amphipathic secondary metabolites, which are glycosides of triterpenoids and steroids [18, 19]. Term "saponin" has been derived from the Latin word "*sapo*" which means soap, as saponins have foaming properties [20]. Each saponin consists of two parts: a hydrophilic sugar moiety such as glucose, arabinose, rhamnose, xylose and glucuronic acid; and a lipophilic steroid or triterpenoid aglycone moiety or sapogenin [19, 21] (Fig. **1**). Structures of some steroid and triterpenoid saponins are presented in Table **1** [22].

Vicken *et al.* [23] and Faizal and Geelan [24] explained that steroidal and trietrpenoid saponins are found mainly in plants belonging to the classes Magnoliopsida and Liliopsida, respectively. The main plant families from Magnoliopsida and Liliopsida which contain saponins are Araliaceae, Campanulaceae, Dioscoreaceae, Leguminosae, Liliaceae, Polygalaceae and Scrophulariaceae [22]. Based on the carbon skeleton of the aglycone moiety,

saponins can be classified into 12 major groups such as, steroids, dammaranes, lupanes, taraxasteranes, tirucallanes, oleananes, cycloartanes, hopanes, ursanes, cucurbitanes, lanostanes and 23-nor oleananes [23, 24]. Some plant products rich in saponins are legume seeds, asparagus, ginseng roots, yam seeds, liquorice roots, sunflower seeds, yucca, sugar beet, tea leaves, tomato seeds, capsicum peppers, spinach leaves, oats, quinoaseeds, fenugreek seeds and *Allium* species [25]. Other than plants, saponins are found in fungi and some marine organisms *e.g.*, starfish, sponges and sea cucumbers, *etc*. also [19, 26]. Saponins give a pungent and bitter taste to plants [27]. Saponins possess both polar and non-polar moieties, *i.e.*, sugar and sapogenin, therefore, they are surface-active and have foaming capacity [28]. pH can affect the stability of saponins, however, they are are not affected by heating, therefore, normal cooking does not reduces their biological activities [29].

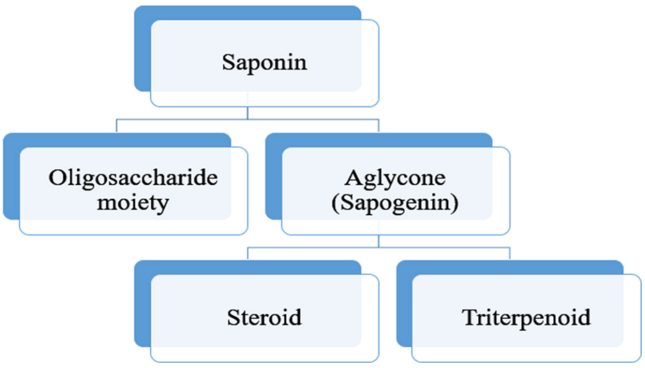
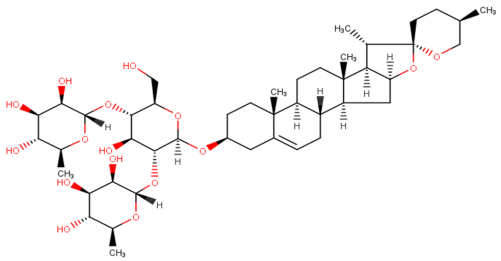


Fig. (1). Composition of a Saponin.

Table 1. Structures of some steroidal and triterpenoid saponins [22].

A. Steroidal Saponins
 **(a) Dioscin**

CHAPTER 10

Chemomodulatory Potential of Lutein Derived from Dietary Sources

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Abstract: The mortality rate from various types of cancer is unacceptably high till date. Although, there is a huge advancement in understanding the diverse mechanisms of carcinogenesis and the development of potential drug leads, still there are massive mortality rates. The consumption of various green/yellow vegetables and fruits can help in reducing the risk of cancer. There is a plethora of potential anticancer compounds present in green leafy vegetables, which have been extensively evaluated in cancer. Various anticancer leads include dietary agents in which carotenoids are very significant in combating cancer. Lutein is a yellow carotenoid present in vegetables and fruits. It is the second most prevalent carotenoid in human serum, and its consumption is beneficial for promoting good health. The nutritional value of lutein is very high, and besides this, it is reported to exert antiproliferative potential against various cancers such as cervical, skin, lung, breast and colon cancer. Lutein stimulates various genes involved in T-cell transformations that are activated by mitigens, cytokines and antigens, thereby acting as anti-cancer. Lutein can oxidize and degrade easily due to the presence of conjugated bonds in its isoprenoid polymeric structure. Various food processing techniques can also affect the integrity of lutein. Therefore, there has been development of novel drug delivery systems to enhance the absorption andbioavailability of lutein and also to prevent its chemical degradation. Therefore, it can be concluded that lutein can serve as an effective agent in chemoprevention to fight against various forms of cancer because of its nutritional value.

Keywords: Carcinogenesis, Carotenoids, Chemoprevention, Dietary agents, Lutein.

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INTRODUCTION

Mortality that results from the common forms of cancer is still unacceptably high. Despite immense advances in the understanding of the mechanisms of carcinogenesis in bringing potent new drugs to the clinic and in treating several relatively rare forms of cancer, overall mortality statistics are unlikely to change in a fundamental way. There has been a re-orientation of emphasis in cancer research that will direct greater resources towards the prevention of new disease, rather than the treatment of end-stage diseases [1]. Various epidemiological studies have reported that the consumption of green/yellow vegetables and fruits can reduce the risk of cancer. Green leafy vegetables contain a wealth of potential chemopreventive compounds. These fruits and vegetables have been investigated extensively for anticancer agents due to the presence of lutein in abundance [2]. Carotenoids are mainly present in the chloroplast of plant cells and are important tetraterpenoid organic pigments. Lutein [(3R,3R, 6R) β,ε-carotene-3-3-diol] is a yellow carotenoid present in many commonly eaten fruits and vegetables. Carotenoid lutein is mainly found in the macular region of the retina in the eyes. It helps in the regulation of vision and visual acuity [3]. Lutein is the second most prevalent carotenoid in human serum. It is reported that taking 5-12 mg lutein daily is beneficial for positive health effects [4]. This book chapter provides insight into the most recent data on lutein and its role in the prevention of various cancer types.

LUTEIN AND ITS SOURCES

Lutein belongs to the family xanthophyll and is a common carotenoid present in bacteria, algae, yeasts and plants [5]. The pure form of lutein is β, ε-carotene-3, 3′-diol ($C_{40}H_{56}O_2$), and it appear as a yellow-orange crystalline, lipophilic solid (Fig **1**). Lutein contains conjugated carbon-carbon double bonds, which facilitate the movement of free electrons and allow the light to absorb in the blue section of the visible spectrum producing strong yellow-orange color [6, 7]. The prominent application of lutein is the color brightening of poultry feathers and deepening the yellow color of egg yolk [8]. Due to the pleasant yellow color of lutein, it has been widely used as a natural food colorant [9].

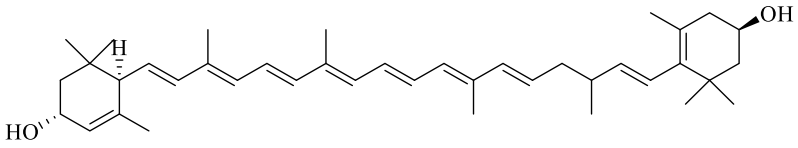

Fig. (1). Chemical structure of Lutein.

FOOD SOURCES OF LUTEIN

Chicken egg yolk is an excellent source of lutein due to its high-fat content and high bioavailability [10 - 13]. The various sources of lutein in various plant and food sources are represented in Table **1** [14].

Table 1. Sources of Lutein.

Source	Scientific Name	Content (µg/100 g)	References
American gooseberry	*Pereskia aculeata Mill*	250-290	[15]
Araza	*Eugenia stipitata McVaugh*	154-756	[16]
Black palm	*Astrocaryum standleyaum*	410-470	[17]
Broccoli	*Brassica oleracea*	3110-3960	[18]
Caryocarvillosum	*Caryocar villosum*	70-110	[19]
Cashew	*Anacardium occidentale*	20-40	[17]
Cilantro	*Coriander sativum*	7703	[20]
Guava	*Psidium guajava L. var. Regional roja*	3-11	[21]
Jackfruit	*Artocarpus heterophyllus*	10.36-55.61	[22]
Kale	*Brassica oleracea L. var.acephala*	2860-3500	[18]
Lettuce	*Lactuca sativa L. (Mini Romaine - Marta)*	1290-1690	[23]
Maize	*Zea mays Amarelao 3*	587-593	[24]
Pepper	*Capsicum annuum L. (F1 AmandaHybrid)*	670-830	[25]
Pitanga	*Eugenia uniflora L.*	120-310	[26]
Potato	*Solanum tuberosum* subsp. *Phureja*	135.2-152.4	[27]
Pumpkin	*Cucurbita maxima*	623	[28]
Sweet Potato	*Ipomoea batatas Lam. CNPH 1194*	1100	[29]
Tree Tomato	*Solanum bataceum*	120-130	[30]
White bryony	*Bryonia dioica*	19,130	[31]
Marigold flower	*Tagetes erecta*	21,600-97,600	[32]
Microalgae	*Chlorella fusca*	420,000-470,000	[33]

As shown in Table **1**, lutein content has been mainly found in dark green vegetables such as broccoli, lettuce, cilantro and kale (1290-7703 µg/100 g of plant material) [34]. However, lutein content is less in fruits with higher water content, such as guava and jackfruit, containing 3-55.61 µg of lutein/100 g of the source [35].

CHAPTER 11

Potential of Biomaterials Derived from Marine Algae as Anticancer Agent

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Abstract: Cancer is one of the most serious and common human diseases, causing millions of deaths per year worldwide. Currently, the discovery of noble therapeutic agents with a natural origin for cancer treatment is a major challenge. In this context, marine algae with wide species and phytochemical diversity will offer great scope for the discovery of new drugs. Algae with marine origin, including microalgae and macroalgae (seaweeds), constitute more than 90% of oceanic biomass. Marine algae are rich sources of pigments, lipids, carotenoids, omega-3 fatty acids, polysaccharides, vitamins and other fine chemicals. The biomaterials obtained from marine algae are important ingredients in many products, including cosmetics and drugs for treating cancer and other diseases. The *in vitro* and *in vivo* evaluations of biomolecules derived from marine algae have shown a vast range of pharmacological properties such as antioxidant, immunostimulatory and antitumor activities to control cancer. In spite of the rich source of various bioactive molecules, the marine algal flora largely remains unexplored for the discovery of active molecules against cancer to date. Hence, this review consolidates the available information on marine algae-derived anticancer molecules to provide baseline information for promoting anticancer research based on biomaterials derived from marine algae.

Keywords: Anticancer, Antitumor, Biomaterials, Cancer, Marine algae.

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INTRODUCTION

Cancer is one of the most life-threatening and death-causing diseases with a strong social and economic impact [1 - 3]. Currently, cancer causes 13% of all deaths globally. According to World Health Organization (WHO), there will be 21 million new cancer cases and more than 13 million deaths due to this disease by 2030 [3, 4]. Cancers are the results of an abnormal proliferation of cells due to DNA damage and genomic instability, which is caused by various factors such as biological or internal (age, gender, inherited genetic defects and type of skin), environmental (UV radiation, exposure to chemical or pollutants), and lifestyle-related (diet, stress, obesity, and physical inactivity) factors [5 - 9]. These factors act in a step-by-step sequence or together to trigger cancers in a number of cases [7, 10, 11]. The continuous progress in biological, immunotherapy and modern drug designing has made the cure for cancer a feasible goal [3, 12]. Although, currently available anticancer drugs and therapies can expand the survival time of patients, but these have substantial side effects [2, 13, 14]. In the last few decades, the number of therapeutic agents with natural origin have been exploited for the development of a safer anticancer drug with their cell selective and fewer adverse effects [15].

It has been estimated that more than 60% of the approved drugs for the treatment of cancer are obtained from products of natural origins [15, 16]. According to the reports, nearly 1355 drugs were approved for therapeutic applications from 1981 to 2010; among these, 128 were anticancer drugs, of which 35% were developed from either the natural product or compound extracted from natural products [3, 17]. Traditionally, terrestrial plants have been the main sources of pharmaceutically effective natural products, and plant-derived agents, such as VBL and vincristine (VCR), etoposide, paclitaxel (Taxol®), docetaxel, topotecan, and irinotecan, are among the most effective cancer chemotherapeutics currently available in the anticancer area [16, 18]. Although, the ocean covers more than 70% of Earth's surface with high biodiversity (95% of world biodiversity) and holds a specific habitat for a number of marine species full of natural pharmaceutical components of potential significance, the development of marine natural products is still in its emergent stage [3, 15]. However, attempts have been made in the last few decades to extraction of natural products for drug formulation and till now, more than 18,000 natural products of marine origins have been reported of which nearly 3000 are new anti-cancer compounds [3, 19, 20]. Among marine organisms, bacteria, fungi, actinobacteria, algae (seaweeds), and sponges have been exploited for their potential medicinal applications throughout the world [21]. It is notable that among the scientifically developed marine compounds, although many have entered clinical trials in cancer, to date, only four compounds have been approved for cancer treatment, such as cytarabine

(Cytosar), trabectedin (Yondelis), eribulin mesylate (Halaven) and the conjugated antibody brentuximab vedotin (Acentris) (Mondal *et al.*, 2020).

Among marine organisms, algae are economically and ecologically important resources of the ocean [22 - 24]. Algae are photosynthetic organisms and can be categorized into marine and fresh water. There are three main categories of marine algae on the basis of their pigment colouration as Green algae (Chlorophyta), Brown algae (Phaeophyta), Red algae (Rhodophyta) and two minor categories like Blue-green algae (Cyanophyceae) and Diatoms (Bacillariophyceae) [25, 26]. Marine algae occur as unicellular, colonial, filamentous, heterotrichous and parenchymatous tissue. Their size ranges from microscopic cells to huge plants more than 700 feet, as in the case of *Laminaria* and *Macrocystis* [27]. The large-size multicellular algae are called macroalgae (seaweed) which are visible by the naked eye, while the microscopic single-cell algae called microalgae, which may be prokaryotic or eukaryotic. These organisms can be found attached to the bottom, in comparatively seaside water areas up to 180 m of deepness, on a solid substrate such as dead corals, rocks, shells, pebbles and plants. Huge rocks can serve as an excellent substrate for algae to attach and grow [28]. The distribution of these marine organisms depends on the type of open sea ecosystem, such as pelagic environment, epipelagic environment, mesopelagic zone, bathypelagic zone, abyssopelagic zone, and benthic environment. These diversified divisions of the aquatic world harbour heterogeneous species of algae marine. The images of a few dominant marine algal forms are given in Figs. (**1** and **2**).

Algae have different amounts of lipids, carbohydrates, proteins, nucleic acids, pigments, vitamins, minerals, and polysaccharides according to species and growth conditions (Fig. **3**). These compounds proved to possess a wide range of nutritional and functional value apart from their potential use as therapeutic agents in a biomedical area [24]. Further, the tolerance of marine algae to a broad range of adverse environmental conditions such as temperature, salinity, nutrients, oxygen, solar energy, water clarity, tides, waves, aerial exposure and current has immensely influenced the production and secretion of marine metabolites/ bioactive chemical compounds from these organisms and leads them to be good candidates for drug discovery [2, 3]. Marine algae are a promising prolific source of structurally unique natural products with biomedical potential. Moreover, algae have been revealed as a major source of new bioactive compounds of marine origin, after sponges, microorganisms and phytoplankton. In the last five decades, it is estimated that more than 3,000 natural products have been discovered from algae, and the antitumor activity is one of the most promising among all of the biological activities observed [24].

CHAPTER 12

Biomarkers as Tools for the Early Detection of Cancer

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Abstract: Every year, millions of people around the world lose their lives to different types of cancer, mostly in developing countries. The foremost challenge for the human race in to fight against cancer is its early detection, followed by the appropriate treatment. Currently, one of the most promising and dynamic strategies for early cancer diagnostics as well as for therapeutics, is the use of cancer biomarkers. Generally, biomarkers represent changes in the constituents or composition of cells, tissues, or body fluids, offering a means for comparable classification of diseases as well as the risk factor involved, and thereby providing information about the underlying pathogenesis of the disease. Similarly, a cancer biomarker (CB) is defined as a 'molecular signature' that can potentially provide valid information regarding staging as well as the mechanisms underlying the origin of cancer. Cancer biomarkers (CB) are biomolecules synthesized either by the cancer cells or by other cells of the body in response to cancer. Every cell type has its distinctive molecular signature and recognizable features, such as levels or activities of the myriad of genes, proteins, or other molecular characteristics; therefore, cancer biomarkers can facilitate the molecular definition of cancer. Endoscopy, X-rays, magnetic resonance imaging, computed tomography, invasive tissue biopsies, *etc.*, are the traditional cancer diagnostic methods. However, the use of biomarkers as cancer screening tools have several advantages over these traditional approaches. The emergence of "omics" technologies, like metabolomics, genomics, epigenomics, proteomics, *etc.*, has led to an increase in the number of potentially investigated biomarkers, such as DNA, RNA, miRNA, or other protein biomolecules. In this chapter, we have summarized the importance of biomarkers as powerful and dynamic tools for the early diagnosis of various types of cancers, the phases in the biomarker discovery, the criteria for the selection of biomarkers, the advantages of their preference over traditional methods, various categories of cancer biomarkers, examples of cancer biomarkers currently in use and the future prospectives.

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Keywords: Biomarkers, Cancer, Circulating tumor cells, Diagnosis, Exosomes, Metastasis, MiRNA, Prognosis, Specificity.

INTRODUCTION

Cancer is one of the major health concerns in the present world, and solely in the United States, it is the second leading cause of death. The early or treatable stage for the detection of cancer is still one of the greatest challenges in clinical practice. With a remarkable increase in the understanding of the biology of cancer and the speedy advancements in molecular technology that have occurred in the recent past, studies related to cancer biomarkers are published almost daily. A biological marker or biomarker is defined as a "*characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological response to a therapeutic intervention*" [1]. Such characteristics can be cellular, biochemical or molecular (including genetic and epigenetic). Biomarkers play a key role in the comparative categorization of diseases and the associated risk factors by presenting variations in the constituents at cellular, tissue, or body fluid level. Likewise, a cancer biomarker is a 'molecular signature', providing valid information about the origin of cancer, staging, and tumor progression. In the case of cancers, biomarkers are either produced by the tumor cell itself or by other non-cancerous cells or tissues of the body in response to the tumor [2]. Cancer cells show wide spectrum genetic alterations, including point mutations, gene rearrangements, and gene amplification which in turn causes disturbance in several molecular pathways responsible for survival, cell growth, and metastasis. When these changes are reported in the majority of the patients concerning a specific tumor type, these could be used as a diagnostic or prognostic biomarker to monitor a therapeutic response [3]. A large number of biological molecules, including proteins, peptides, nucleic acids, antibodies, extracellular vesicles, and some cellular processes, *viz.* apoptosis, angiogenesis, or proliferation, can serve as cancer biomarkers. Based on their locations inside the body, biomarkers have been categorized as non-invasive, minimally invasive, or invasive. Biomarkers sampled either from exhaled breath or from body fluids like saliva or urine without causing any harm or inconvenience to the patients are said to be non-invasive biomarkers. Minimally invasive biomarkers are those which are sampled through procedures like a blood draw or finger pricking. Biomarkers sampled*via*tissue biopsies are considered invasive biomarkers as these require complex procedures [2, 4, 5]. Biomarkers could be subjected to the assessment of patients in different clinical settings, including risk estimation of disease, primary cancer screening, differentiating malignant from benign findings, distinguishing different types of malignancies, estimating prognosis and prediction for patients diagnosed with cancer, and monitoring disease status, either to find recurrence or measure

response to follow up therapy [5]. Further, biomarkers also possess the potential to do well in other functions like speeding up the drug development process, reduction of exposure to ineffective experimental treatments, and so on. In 2017, the U.S. Food and Drug Administration (FDA) officially approved its first drug, namely 'Keytruda (pembrolizumab)', based on tumor biomarkers rather than the location in the body where the tumor originated [6]. Currently, genomic technologies such as DNA microarrays, PCR-based assays, and FISH (fluorescence in situ hybridization); proteomic approaches like 2-dimensional gel electrophoresis (2-DE) and different forms of mass spectrometry (MS). Analytical metabolomic approaches like gas-liquid chromatography (GLC), nuclear magnetic resonance spectroscopy (NMR), high-performance liquid chromatography (HPLC), and MS, allow researchers and clinicians to have a simultaneous, high-throughput and robust diagnosis, assessment, and monitoring of various genetic, epigenetic or proteomic biomarkers responsible for carcinogenic transformation [7] (Fig. **1**).

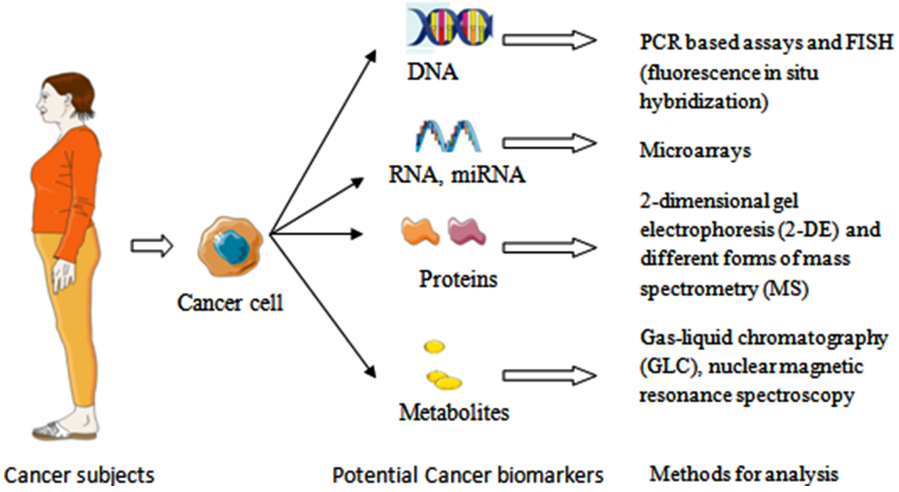

Fig. (1). Approaches for the detection and analysis of different potential cancer biomarkers.

Two main statistical characteristics define the clinical performance or efficacy of a biomarker. These characteristics are sensitivity and specificity. In the context of cancer, sensitivity, also known as true positive rate (TPR), indicates the proportion of subjects with cancer who test positive, while specificity or true negative rate (TNR) indicates the proportion of subjects without cancer who test negative. In other words, the probability that a particular cancer biomarker under assessment will be detected positive in cancer-carrying subjects represents its sensitivity, and on the other hand, the probability of a particular cancer biomarker being either absent or being present at a level less than the threshold value in non-cancer subjects represents its specificity [8, 9]. As such ideal diagnostic should

CHAPTER 13

Biomarkers for the Diagnosis and Surveillance of Cancer

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Abstract: Cancer remains one of the leading causes of death worldwide. Cancer management has been a daunting task for both health professionals and patients throughout the journey. Screening of cancer at the right time/stage remains the most critical part of the riddle. Certain molecules that characterize cancer, known as 'biomarkers,' come out to be the most useful in this journey. The National Institute of Health defines a biomarker as "a characteristic used to measure and evaluate objectively normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention". These have proven to be often easily available agents employing minimally invasive methods. Biomarkers have played crucial roles in screening, asymptomatic and early-stage detection, monitoring of the treatment therapy and eventual follow-up to check upon a probable re-lapse or metastasis. A cancer biomarker can be any of the biomolecules such as protein, DNA, RNA, proteoglycans, immunological compounds, salivary biomarkers and endogenous peptides. With the refinement in high-throughput techniques, the list of the types of biomolecules and the number of potential biomarkers is only increasing, with volatile organic compounds from the breath (breath biopsy) adding to the list. In this chapter, we shall put effort into reviewing this otherwise very vast topic. The chapter will outline various types of biomarkers, the journey so far with clinically approved cancer biomarkers, the challenges being faced, and conclude with future perspectives.

Keywords: Biomarkers, Cancer, miRNA, Proteomics, Tumor DNA, Tumor metabolomics.

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INTRODUCTION

According to GLOBOCAN statistics, there were around 18.1 million cancer patients worldwide, with 9.6 million deaths in 2018. An appalling number of 1 in 5 men and 1 in 6 women would develop one or the other type of cancer throughout their lifetime, as estimated by International Agency for Research on Cancer (IACR) [1]. Around 200 different types of cancer have been identified as responsible for 1500 deaths occurring each day worldwide [2]. Rapidly increasing cancer cases have emphasized the need for early detection, appropriate therapy and cure of cancer through cancer screening, prognostic determination and monitoring to ameliorate the cancer burden. The past several decades have been witness to the considerable research investment being put in by researchers all over the world for the early detection of cancer. Diagnosis of early-stage cancer as asymptomatic malignancies and even as premalignant lesions can be attributed to the changes in the clinical practices leading to more efficient screening [3]. In certain regions, the scaled-up prevention measures have started to pay off with lower incidence rates [1]. High hopes reside on cancer biomarkers to help reduce cancer burden by assisting in timely detection, prognosis, validation of appropriate treatment line and monitoring a probable relapse [4].

An ideal cancer biomarker or tumor marker should be a protein, protein fragment, nucleic acid, or a hormone present in the blood, urine, or other body fluids of the cancer patient but not visible in the normal individual [5]. National Cancer Institute defines a bio-marker as a biological molecule detected in the blood or other body fluids that manifests an abnormal process, condition, or disease such as cancer (https://www.cancer.gov). A tremendous variety is seen in the bio-markers, which may include nucleic acids (micro-RNAs, non-coding RNAs), over-expressed proteins (an enzyme or receptors), hormones, peptides and antibodies. Thus, a bio-marker is a collection of altered gene expression and metabolomic and proteomic signatures [6].

In this book chapter, we are trying to underline the significance of biomarkers while understanding their core roles, journey to development, and various types. With the discussion of currently used cancer biomarkers, we shall address the challenges ahead for cancer biomarkers.

JOURNEY OF CANCER BIOMARKERS

It may come as a surprise that the earliest reported use of cancer biomarkers was by Egyptians around 2000 years ago [7]. In modern-day medicine, it started with Bence Jones proteins around 170 years ago [8]. By 1988, Bence Jones proteins had secured their United States - Food and Drug Administration (US-FDA), USA

approval for immunodiagnostic tests for a number of cancers [4]. This was followed by serum amylase, carcinoembryonic antigen (CEA), CA 19-9, CA 15-3, and CA 125 and the list is ever-growing [3, 4]. Today, Prostate Specific Antigen (PSA) stands tall amongst all the cancer biomarkers as the first US-FDA-approved biomarker for the screening of cancer [9] by contributing towards dramatically increased early detection of prostate cancer in patients [10]. As early as in the mid-1930s, the significance of early detection was understood as "Early is the watchword for cancer control, early diagnosis, early treatment will save many lives" as a slogan in one of the posters collected under Work Projects Administration Poster Collection in the USA (www.loc.gov/pictures/resource/cph.3b48900). Even today, around 90 years later, 'Early' remains the watchword!

Most cancer screening or detection methods currently in use are unable to detect early-stage cancer and most are concentrated on late-stage or fully developed cancer. The screening for cancer at an early stage suffers from the drawback that the cancer disease is a heterogeneous condition, comprising many different phenotypes biologically and thus needing different ways for therapeutic interventions. This has complicated the issue for the development of a suitable bio-marker for cancer, hence to address the heterogeneity problem with cancer disease, the development of the bio-marker through proteomic, genomic and metabolomic means seems promising.

The emergence of the new branch of the life science known as "omics" comprising of genomics, epigenomics, transcriptomics, proteomics and metabolomics, has broadened the field for the search for the new and novel cancer bio-markers with a distinct advantage over the currently used bio-markers with better treatment interventions [11, 12]. At least 350 genes out of ~22,000 protein-coding genes in the human genome with somatic mutations show strong evidence for cancer progression. The signaling pathway genes along with the regularly mutated genes in cancer, seem to offer a better diagnostic potential than relying on mutation studies from a single dysregulated gene. The cytogenetic diagnosis seems to play an important role in the early detection of cancer, like loss of the long arm of chromosome 18 is associated with colorectal cancer, since the long arm of chromosome 18 is home to many of the tumor suppressor genes such as *SMAD2*, *SMAD4* and *SMAD7* which are transcriptional mediators in the TGF-β signaling pathways [13, 14]. Epigenomics is rapidly evolving as a possible detection method for early-stage cancer. It involves heritable changes in the gene expression not attributable to the changes in the genome sequence. Epigenetic modifications include histone modifications, DNA methylations and long non-coding RNAs. The epigenetic modifications appear early during human malignancies and hence can be utilized in the early-stage diagnosis of cancer [15]. The proteomic approach to identifying early-stage cancer basically identifies the

CHAPTER 14

Animal Models used in Cancer Research: Role of Transgenic Animals

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Abstract: In spite of the existence of many chronic diseases, cancer is still one of the major distresses for public health and is also the second largest major concern of death. The data collected from the last 50 years of research showed that very few cancers are curable, and the fear factor related to this disease is still unaltered. Victorious bench-to-bedside transformation of basic methodical findings about cancer into therapeutic involvements for patients relies on the appropriate selection of animal experimental models. Animal models play an important role in studying the genetics and biology of human cancers as well as the preclinical examination of various cancer therapeutics and cancer prevention. In this chapter, we will review the imperative animal models such as spontaneous tumour models, chemically induced tumour models, radiation-induced tumour models, *etc*., along with other animal models, such as porcine, canines, *etc*., used for immuno-oncological research. In addition, the role of transgenic animals in cancer research will also be discussed.

Keywords: Adenoviruses, Animal models, Cancer, Canines, Fishes, Herpesviruses, Porcines, Spontaneous tumour models, Transgenic animal models.

INTRODUCTION

Cancer development occurs in different steps, and the cells in the body undergo numerous changes in their characteristics [1] (Fig. **1**). It is the foremost cause of death worldwide and poses a great burden on society [2, 3]. In recent years, although several methods have been available for the prevention and treatment of certain cancers, it still needs great input from the scientific community [4 - 6]. The primary screening method used in cancer research is the use of cell lines, but *in vivo* models are obligatory.

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The selection of animal models has contributed considerably to our understanding in the field of cancer research as these represent human disease as closely as possible. Animal models act as significant tools to explore the pathogenesis and develop various treatment approaches for cancer in humans [7]. Clinically and biologically, these models play an important role in exploring the succession of diseases and the amplification of therapeutic procedures.

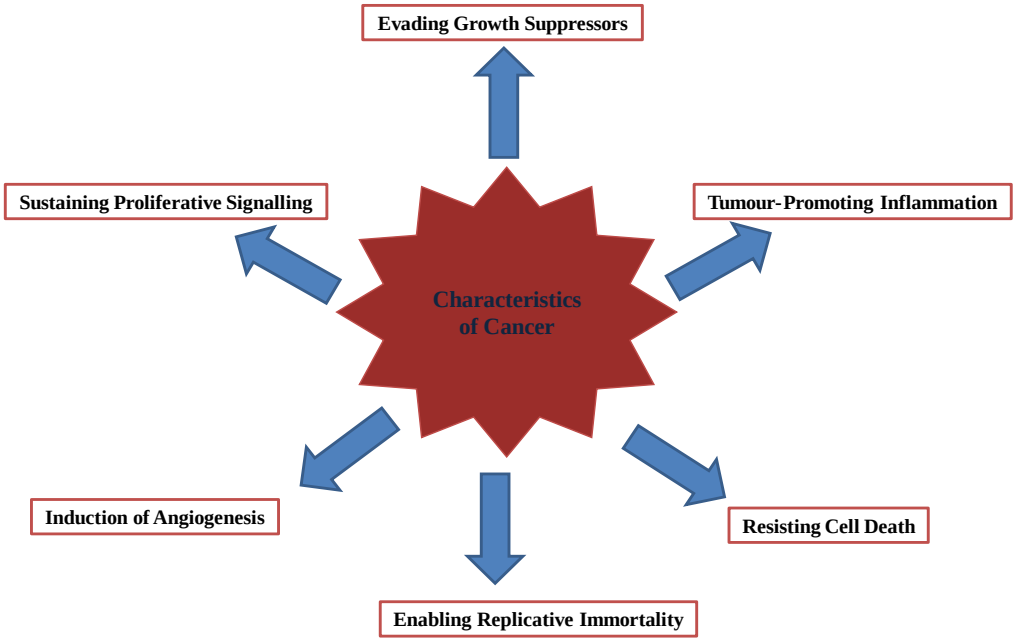

Fig. (1). Important characteristics of cancer.

Animal models are divided into three parts:

1. Exploratory models: These models play an important role in understanding a biological mechanism.
2. Explanatory models: More or less complex biological problems are studied by these models. The models may also be physical or numerical model systems explored to disentangle complex mechanisms.
3. Predictive models: These models are used to ascertain and enumerate the impact of a treatment.

The various animal models used in cancer research are reviewed briefly in Fig. (**2**).

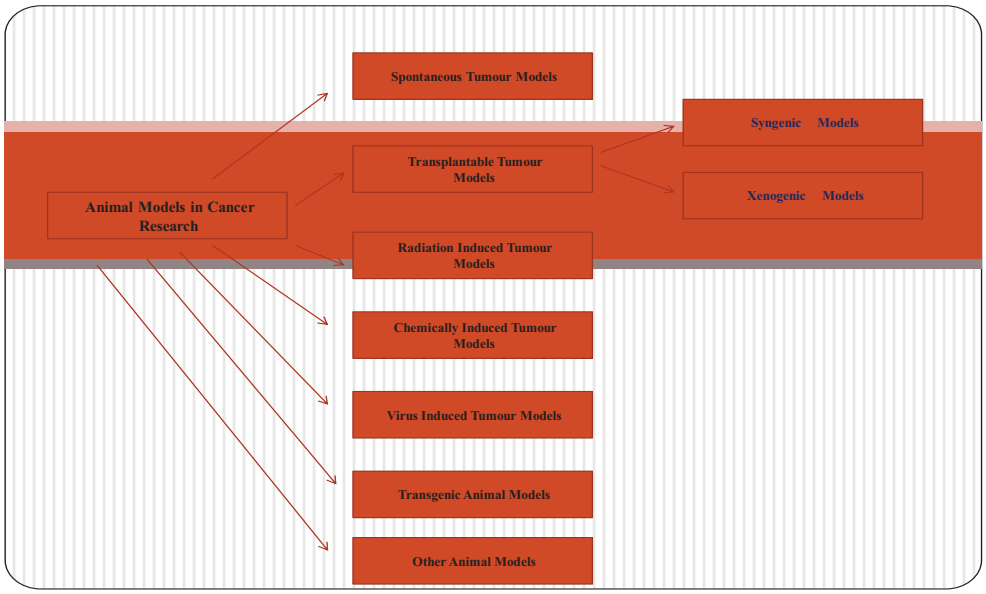

Fig. (2). Animal models used in cancer research.

SPONTANEOUS TUMOUR MODELS

Extensive literature is available on these models, but the Athymic nude mouse, acts as the best-known organism. The gap stuck between simple *in vivo* tumour model and this model fills human scientific trials. In the case of human disease, these models are performed using naturally stirring genetic mutants (variants). The application of the Athymic nude mouse characterised an innovative invention in the study of hetero-transplanted tumours that facilitated the first depiction of natural killer cells [8]. The various mutants of these models are available in inbred strains with equivalent congenic or coisogenic strains that are accountable to develop discrete forms of cancers, including mammary cancer, leukemia, head and neck carcinoma, lung carcinoma, hepatomas and pulmonary adenomas [9]. These models resemble human cancers in antigenicity and kinetics.

TRANSPLANTABLE TUMOUR MODELS

Over the last 30 years, transplantable tumour models played a pivotal role in cancer research as they are based on the use of cancer cell lines or tissues in rats or mice. These models can be categorised into two types:

- Syngenic models
- Xenogenic models

CHAPTER 15

Stem Cell Models: Novel Experimental Approach for Testable Alternatives against Therapy-resistant Breast and Colon Cancer

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Abstract: Breast and colon cancer represent the leading causes of mortality in developed countries. The treatment options for these organ site cancers differ depending on the status of hormone/growth factor receptors in molecular subtypes that exhibit altered expression of oncogenes/tumor suppressor genes and growth factor-mediated molecular pathways. Conventional cytotoxic chemo-endocrine therapy traditionally includes the use of anthracyclin, taxol, cisplatin, anti-estrogens, anti-folates and DNA anti-metabolites. Additionally, the use of molecular pathway-specific small molecule inhibitors represents evidence-based targeted therapy. Long-term conventional or targeted therapy using pharmacological agents is frequently associated with systemic toxicity, acquired tumor resistance and the emergence of drug-resistant cancer stem cells. These limitations are associated with the progression of the therapy-resistant disease.

Natural products such as dietary phytochemicals, their respective bioactive agents, botanicals, nutraceuticals and nutritional herbs are widely used in complementary and alternative medicine in women for estrogen-related issues, osteoporosis and breast diseases. Unlike conventional or targeted chemo-endocrine therapeutics, natural products, mainly due to their low systemic toxicity, may not lead to acquired tumor resistance and therefore, represent testable alternatives against therapy-resistant cancer.

These aspects emphasize a need to develop reliable experimental approaches, and specific and sensitive biomarkers that facilitate the identification of effective testable alternatives against therapy-resistant cancer.

Models for drug-resistant stem cells have been developed and characterized from the parental breast and colon carcinoma-derived cell lines, as well as from the cell lines derived from genetically predisposed colon cancer models. These stem cell models are characterized by the quantifiable expression status of select stem cell-specific cellular and molecular markers.

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Mechanistically distinct natural products have documented growth-inhibitory effects on parental cell lines. Some of these agents also exhibit stem cell targeted growth inhibitory efficacy.

Recognizing clinical evidence for the role of estrogens in breast and colon cancer, future investigations include the development of tumor organoid models of therapy-resistant breast and colon cancer from female patient-derived xenografts. These investigations support a scientifically robust rationale to provide clinical translatability for patient-derived preclinical data.

This chapter summarizes the evidence relevant to experimental models systems, natural products and efficacy of lead compounds as stem cell-targeted testable alternatives against breast and colon cancer. Collectively, discussed evidence and its clinical relevance support the hypothesis that natural products may benefit patients that are diagnosed for therapy resistant cancers.

Keywords: Breast and colon cancer, Drug-resistant stem cells, Naturally occurring substances, Preclinical cellular models.

INTRODUCTION

Epithelial organ site cancers of the breast and colon together represent major cancer types in women. The American Cancer Society projects combined new cancers in 328,750 women and cancer-related deaths in 66,740 women for these organ site cancers in 2021 [1]. Published evidence from clinical and preclinical data has suggested that, similar to breast cancer, status of the ovarian steroid hormone, estradiol, may also function as an important endocrine factor in colon cancer [2, 3].

Traditional pathological staging of breast and colon cancer using tumor size, nodal involvement and localized/distant metastasis (TNM system) and immuno-histochemical assessment of hormone/growth factor receptors together continue to play an important role in clinical pathology. In addition, global gene expression profiling of tumor samples has provided a molecular classification of tumor subtypes [4 - 6]. Based on their genetic, molecular and hormonal status, these organ site cancers are classified as Luminal A, Luminal B, HER-2-enriched and triple-negative for breast cancer, and genetically predisposed familial adenomatous polyposis (FAP), hereditary non-polyposis colon cancer (HNPCC) models and sporadic colon cancer subtypes. Collectively, these aspects represent a basis for the evidence-based selection of appropriate therapeutic options.

At the mechanistic level, genetic alterations in oncogenes HER-2, Myc, RAS, and RAF, and in tumor suppressor genes BRCA-1, BRCA-2, APC and p53 play a crucial role in the initiation and progression of genetically predisposed as well as sporadic breast and colon cancers [5, 6]. HER-2, Myc and RAS transgenic animal

models exhibit an increased incidence of breast cancer [7], and those with defective Apc tumor suppressor gene expression or DNA mismatch repair gene expression exhibit an increased incidence of intestinal neoplasia [8 - 10]. Gain of function mutations in oncogenes and loss of mutations in tumor suppressor genes are associated with a genetic predisposition for breast and colon cancers. The cellular models for breast and colon cancer offer relevant experimental approaches that complement genetically predisposed clinical breast and colon cancer, and thereby, facilitate investigations on the role of gene-environment interaction [11]. Cellular models expressing these genetic defects may also provide novel experimental approaches to examine gene-environment interaction in cancer stem cell biology relevant to the identification of potential molecular mechanisms for targeted therapy [12, 13].

Preclinical *in vivo* animal studies represent well-established experimental approaches for lead compound efficacy. For example, the 850^{MIN}/+ animal model for the adenomatous polyposis coli (Apc) tumor suppressor gene-related familial adenomatous polyposis (FAP) syndrome has been widely used to evaluate lead compound efficacy as single agents as well as combinations of mechanistically distinct multiple agents [7].

Clinically relevant epithelial cell culture models facilitate mechanism-based investigations directly on the target cells and effectively complement *in vivo* approaches. Traditionally, cancer stem cells are isolated from carcinoma-derived cell lines. Several assays for the isolation and characterization of stem cells have been extensively published. These optimized assays include i) Separation of "side population" of cells based on drug efflux, ii) Expansion of cells from anchorage-independent colonies, iii) Separation of cells positive for cell membrane-specific antibodies, and iv) Expansion of cells resistant to chemo-endocrine therapeutics. The widely used drug-resistance assay for the isolation and characterization of cancer stem cells is relevant to drug-resistant stem cells from therapy-resistant clinical cancer subtypes. These drug-resistant cancers stem cell models facilitate the identification of efficacious testable alternatives.

Therapeutic options for breast and colon cancer include conventional chemo-endocrine therapy and targeted therapy based on hormone/growth factor signaling pathways [14 - 17]. Pharmacological agents used in these therapies are frequently associated with systemic toxicity, acquired drug resistance and the emergence of therapy-resistant cancer stem cells. Unlike pharmacological agents, natural products exhibiting low systemic toxicity may not induce acquired tumor resistance, and therefore, may provide a testable alternative against therapy-resistant breast and colon cancer.

CHAPTER 16

In vitro and *in vivo* Methods used for the Evaluation of Anticancer Secondary Metabolites

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Abstract: Cancer is a large group of diseases that affect the human body at all ages and causes death worldwide. Important progresses have been made in early diagnosis, prevention measures and treatment. Widespread use of secondary metabolites derived from plants has been made for the production of various effective medicines. Various natural bioactive compounds derived from medicinal plants are used as anticancer mediators to remediate cancer syndrome, but they have toxicity and side effects, and hence there is a need to explore more plant-derived cytotoxic chemical agents. Consequently, an effort has been made to evaluate various *in vitro* and *in vivo* methods that are used for assessing the efficiency of the anticancer efficacy of natural bioactive compounds derived from medicinal plants. Anticancer secondary metabolites derived from plants are efficient candidates for *in vivo* and *in vitro* anticancer activity. This chapter provides detailed information on different plant explants and extracts and various methods used to evaluate anticancer activity.

Keywords: Anticancer activity, Anticancer, Cytotoxic, *In vitro*, Secondary metabolites.

INTRODUCTION

Cancer is a serious health challenge worldwide, and as per the World Health Organization (WHO), the global cancer burden is increasing at a rate of 5 million new cases per year. There is no effective treatment for various types of cancers at hand, although immunotherapy and gene therapy has been revealed to be encouraging for the treatment of a number of cancers [1]. There is an urgent need to develop novel drugs with maximum effect and least side effects for the treatment of cancer. Various synthetic and natural compounds have been tried for the treatment of different types of cancers. Secondary metabolites are the natural bioactive compounds derived from plants that are used for the production of vari-

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ous effective medicines. These are efficient candidates for the advancement of pharmaceuticals; subsequently, various bioactive compounds need to be discovered to have positive health effects [2]. They are accumulated in sub-epidermal cells of the different parts of the plants *via* different metabolic pathways of the cells. They have strong communication in-between plants and the atmosphere of their surroundings, protecting them from pathogens, rays of UV light, and different external stimuli, *etc*., and, hence, they play a dynamic role in the survival of plants and the production of secondary metabolites in affected by various factors of the environment [3, 4]. For a long time, research has been focused on extraction, complex structure revelation, and evaluation of the medicinal value of various secondary metabolites. Nearly 70% of secondary anticancer metabolites are derived from medicinal plants [5]. As per the British Broadcasting Corporation (BBC), medicines that are derived from secondary metabolites will reach from $29.3 billion in 2017 to about $39.2 billion in 2022, and the yearly progress percentage will go up to 5.9% [6]. A large number ofanticancer secondary metabolites currently used for anticancer activity are derived from of plant kingdom. The National Cancer Institute (NCI) progressed in a vast screening approach to analyze the efficiency of antitumor potentials of various secondary metabolites derived from plants in the 1960s [7]. Hence, an investigation has been carried out to investigate the potential properties and uses of secondary metabolites for the preparation of anticancer drugs for cancer [3]. Although various anti-cancer secondary metabolites are used as anticancer mediators to remedy the cancer syndrome but they have toxicity and side effects, and hence the investigation is exploring the plant-derived cytotoxic chemical agents [8]. Various secondary metabolites that are extracted from plants are being studied for their efficiency to stop cell division and initiate the programmed cell death of cancerous cells [9]. Some anticancer secondary metabolites like paclitaxel, vinca alkaloids, etoposide, comptothein, vincristine and vinblastine are used for the treatment of leukaemia, testicular teratoma, Hodgkin's disease and many other cancers like breast and ovarian cancers and at present-day, they are most efficient anticancer secondary metabolites [10]. Besides higher efficiency, anticancer agents have well-accustomed side effects for cancer therapy treatment. Consequently, widespread research is mandatory in this field to the quest for anticancer secondary metabolites that can offer value-added treatment deprived of conceding the value of life [11]. Consequently, an effort has been made to evaluate various *in vitro* and *in vivo* methods used to assess the efficiency of the anticancer properties of natural bioactive compounds derived from medicinal plants [12, 13]. Anticancer secondary metabolites derived from plants are efficient candidates for *in vivo* and *in vitro* anticancer activity. This chapter provides detailed information of different explants and extract of plants and various methods used to evaluate anticancer activity.

EVALUATING APPROACHES FOR ANTICANCER ACTIVITY

Sustainability and development of the cells are good signs of healthy cells, and anticancer secondary metabolites affect the metabolic processes of the cell. Various natural bioactive compounds derived from medicinal plants are used as anticancer mediators to remedy cancer syndrome, but they have toxicity and side effects, and hence the investigation is to explore the plant-derived cytotoxic chemical agents. Consequently, an effort has been made to evaluate various *in vitro* and *in vivo* methods that are used for assessing the efficiency of the anticancer properties of a natural bioactive compound derived from medicinal plants. To control apoptosis *via* toxicity, there is a prerequisite for low-cost and efficient *in vitro* and *in vivo* approaches for screening cytotoxicity and cell viability of the cell [14]. Evaluation of cytotoxicity and cell viability is based on the absorptivity of the cell membrane and the production of enzymes [15].

In vitro Approaches

A large number of *in vitro* and *in vivo* approaches have been established to carry out the effectiveness of anticancer secondary metabolites. *In vitro* methods like Trypan blue dye exclusion assay, Lactate dehydrogenase (LDH) assay, MTT assay, XTT assay and Sulforhodamine B assay are most commonly used for assessing the anticancer potential of metabolites from medicinal plants. Amongst all *in vitro* approaches, MTT and Sulforhodamine B assay are the most commonly used methods for assessing anticancer activity [16, 17].

Trypan Blue Dye Exclusion Assay

Trypan blue is a dye used to observe young cells amongst dead cells. Young cells have a cell membrane; trypan blue stains do not enter the cell membrane of young cells and come into the cytoplasm. Trypan blue stain penetrates into the cell membrane and the cytoplasm. The dead cells showed blue color under microscopy [18 - 20]. The trypan blue dye exclusion assay is the greatest frequently used method for the screening of cell viability. In this assay, Hank's Buffered Salt Solution (HBSS) was used for the washing of the cells, initially, the cells were washed away with HBSS and centrifuged at 10,000 for 10 - 15 min rpm. This method is frequently used thrice. The cells are adjourned in the HBSS solution, and the number of cells is accustomed to 2 x 106 cells per ml. The cell suspension is dispended into Eppendorf tubes, and each tube containing 0.1 ml HBSS that accommodates 2 lac cells. The washed cells are treated with medication solution and incubated at 37 °C for 3 hours. After three hours, for the dye exclusion assay, an equivalent amount of the medicated treated cells are assorted with 0.4% trypan blue and set aside for one minute. For counting viable and non-viable cells, treated cells are overloaded in a haemocytometer for two

CHAPTER 17

Nano-based Nutraceuticals and their Applications: Food Safety, Regulation and Challenges

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Abstract: The growth of functional foods has gotten a lot of attention as people become more aware of the relationship between nutrition and human health. Several problems are identified, including discovering beneficial phytochemicals, establishing acceptable consumption levels, and producing suitable food delivery matrices and product compositions. Many nanotechnology-derived processes and materials have the potential to provide innovative solutions in many of those foreparts. Nanotechnology works with materials on the atomic and molecular levels to create structures smaller than 100 nanometers in one dimension. Food nanotechnology could be a comparatively recent area that has opened up an entire world of new applications in the food industry. The applications comprise better taste, color, flavor, texture, and consistency of foodstuffs, the bioavailability of nutraceuticals, increased absorption and health supplements, food antimicrobial developments, food packaging materials with better quality, mechanical barrier, and antimicrobial properties, nano-sensors for traceability and observing the condition of food during transport and storage, encapsulation of food constituents or additives. This chapter briefly reviews the role of nanotechnology in functional foods and its applications, and food safety, regulation, and challenges are discussed.

Keywords: Food nanotechnology, Food supplements, Food applications, Nutraceuticals, Safety regulations.

INTRODUCTION

The term Nanotechnology, as defined by the National Nanotechnology Initiative in 2006, is the understanding and control of matter at dimensions ranging from 1 to 100 nm [1]. A wide variety of nano-techniques and materials are being developed in an attempt to declare greater control over food character traits to improve processing functionalities, like flavor, texture, speed of processing, heat tolerance, shelf life, traceability, safety, the bioavailability of nutrients and cost-

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effective food analysis. The main focus is on functional foods as they provide the power to manage, control and influence the properties of substances that are near to molecular level [2 - 4].

Food items with health advantages are getting increasingly popular as customers become more conscious of the influence of nutrition on their health. As a result, the incorporation of health-promoting components such as essential fatty acids, vitamins, minerals, carotenoids, antioxidants, phytosterol and fibers has gained prominence in the form of so-called functional foods [5 - 8].

Functional foods contain a variety of nutrients and non-nutrients that alter a variety of biological processes related to a state of well-being and health, as well as the risk of disease [9 - 13].

Nonetheless, the addition of these constituents into food formulation may be a difficult task because they are unstable during processing and storage due to their quick degradation (oxidation or hydrolysis) activated by different environmental conditions (temperature, pH, light, oxygen, moisture, *etc*.) and may undergo various unwanted interactions with other food constituents. Some bioactive compounds (polyphenols, peptides, phytochemicals, *etc*.) have a disagreeable odor and flavor, which imparts an unpleasant taste and astringency. Such compounds become unstable due to varied pH ranges and enzymes in the gastrointestinal tract (GIT). Therefore, it is sometimes degraded within the stomach before reaching the small intestine, causing lower bioavailability. Some compounds, like curcumin, essential oils, bioactive lipids, *etc*., are poorly soluble in an aqueous solution, which restricts their application as functional foods [14 - 16].

The FDA defines constituent bioavailability as the amount of increased component concentration that is absorbed within the GIT and reaches the site of action [17]. Bioactive ingredient bioavailability is low due to poor solubility, chemical instability and constituent interactions with other dietary elements [5, 6, 18].

The food sector is valued at over 168 billion dollars and is growing at a rate of approximately 9% every year [13]. The key factors for the current increase in growth include increased access to scientific information about the relationship between food and health. Age-related illnesses are prevalent, particularly in Western nations, and metabolic disorders such as heart disease, obesity, diabetes, and arthritis are on the rise. The food industry has identified several significant challenges to remain relevant and competitive in the field of functional foods, including determining the bioactivity of beneficial substances, determining acceptable consumption levels, and designing appropriate food delivery matrices

and product formulations. This chapter provides an overview of nanotechnology's involvement in functional foods and applications, as well as food safety, regulation, and challenges.

IMPACT OF NANOTECHNOLOGY ON FOOD SUPPLEMENTS

Dietary supplements are often thought to contain minerals, vitamins, fiber, fatty acids, or amino acids, among other food ingredients. Nutrients are necessary for survival, while bioactive molecules do not appear to be necessary because the body can operate without them [19]. However, bioactive compounds may have a health impact and may act as a substitute for direct medication use.

Bioactive Compounds

Bioactive chemicals are nutritional elements found in minute amounts in foods, such as Lactobacillus from yogurt, lycopene from tomato, beta-carotene from carrots, conjugated linoleic acid from cheese, beta-glucan from oats, omega-3 acid from salmon oil, and isoflavones from soybeans. There is evidence that consuming foods high in bioactive compounds is beneficial. Customers are advised to have a diet rich in a variety of vegetables, whole grains, legumes, oils, nuts, and fruits from a practical standpoint [20]. Nanotechnology has shown considerable promise in the realm of functional foods for enhancing the efficiency and dispersion of nutraceuticals and bioactive compounds that promote human health. Nanoencapsulation efforts can result in the protection of micronutrient stability, increased solubility, improved bioavailability, and improved bioactive substances during processing, storage, and distribution [1]. Nanoencapsulation protects bioactive substances from absorption and allows for the regulated release of beneficial living probiotic species at certain gastrointestinal functions. As a result, the viability of probiotic organisms such as Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus rhamnosus, and Bifidobacterium spp. within freeze-dried yogurt is frequently increased by encapsulating this bioactive component with calcium alginate [21]. The bioavailability of antioxidant elements predominantly from tomatoes, notably lycopene, is frequently improved by manufacturing its nanoparticles and adding them to tomato juice, jam, and pasta sauce [22]. Milk protein contains bulky casein, which is utilized to produce nanosized micelles and has been exploited as a vehicle for delivering sensitive health-promoting components, such as vitamins [23]. The electrospinning approach can improve the encapsulation of beta-carotene in biopolymer nanofibers made from zein, which has shown substantial benefits in nanotechnology for food and nutraceutical formulation, bioactive food packaging, and food processing sectors [24]. Hydrolyzed milk protein α-lactalbumin is used

CHAPTER 18

Role of Functional Foods in the Amelioration of Alzheimer's and Related Diseases

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Abstract: Alzheimer's disease (AD) is a neurological illness that causes a person's memory to deteriorate over time, as well as facing difficulties speaking and performing daily tasks. Alzheimer's disease affects around 42 million people worldwide, and this number is expected to quadruple by 2030. A nutraceutical is a bioactive component of human nutrition that is ready to be employed for disease prevention or therapy. The market for nutraceuticals has risen in the recent decade as public awareness of these compounds has grown, as has their utility in the prevention and treatment of a variety of ailments. Antioxidant-rich diets have been found to protect humans from degenerative diseases, such as cancer, diabetes and cardiovascular disease. Plant foods, such as vegetables, fruits, grains, spices, and legumes, have been shown to play important roles in the prevention and treatment of a wide range of chronic diseases by altering many metabolic pathways. Bioactive agents are extra from the functional food and are nutritional elements found naturally in plants that have the potential to have a biological effect. Now, scientists and nutritionists say that the link between nutrition and disease is a relatively recent discovery. The importance of functional foods in the treatment of chronic and neurodegenerative disorders, with a focus on AD, will be highlighted in this chapter.

Keywords: Alzheimer’s disease, Bioactive compounds, Functional food, Nutraceutical, Neurodegenerative disease.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurological illness that causes gradual memory loss and difficulty speaking and performing routine tasks [1]. The annual incidence of this condition ranges from 2 to 4% of the population, ranging from its lowest point between the ages of 65 and 70 to rates approaching 5% for those over the age of 80 [2].

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Alzheimer's disease affects over 42 million people worldwide, and the number could quadruple by 2030. The death of neurons and the breakdown of signaling between neuronal cells in the brain are hallmarks of Alzheimer's disease. Aβ tiny 40 or 42-amino-acid peptide could be the most important component of Aβ plaques [3]. The A, the causal agent in pre-senile dementia, was first proposed around 15 years ago and is now largely accepted by scientists. The most common form of pre-senility and dementia is AD. The human-Amyloid Protein Cleavage Enzyme (BACE-1) could be a major enzyme in the development of amyloid protein plaques, which are linked to Alzheimer's disease progression and symptoms [4].

A nutraceutical is a bioactive component of the human diet that can be used for illness prevention or therapy. Many compounds that become accessible after digestion have additional nutritional benefits; these chemicals are referred to as "bioactive" components. These chemicals have antioxidant, anti-inflammatory, antibacterial, antihypertensive, and anticancer effects, as well as regulating intracellular and extracellular signaling pathways [5]. The nutraceutical market has developed in the recent decade, owing to increased consumer awareness of these chemicals and their potential for disease prevention and treatment [6, 7].

Carbohydrates, proteins, lipids and oils, minerals, vitamins, and organic acids are the most common nutrients found in edible plants. Phytic acid or phytate, tannic acid, tannin, cyanide, and trypsin inhibitors are all anti-nutrients [8, 9].

The concept of using foods to prevent sickness or enhance health is not new in the history of functional food. The technique of supplementing flavor with iodine to prevent goitre in the early 1900s was an early attempt at developing a functional meal. Many foods have been fortified since then, including breakfast cereals, drinkable milk, and grain food [10]. Other foods that have lost a range of nutrients owing to processing are enhanced with the nutrients that have been lost. Bread and bakery items are classic examples of enhanced foods. As technology has advanced, experts have begun to recognize the benefits of a natural balance of healthful meals. Only those crops that have optimal positive nutritional properties are produced now, thanks to advances in gene splicing [11].

Taste, aroma, and nutritional value are all provided by functional foods. Foods are currently being studied in depth for additional physiological effects that may lessen the risk of chronic disease or otherwise improve health. There is no commonly agreed definition of functional foods [12]. The notion was established in Japan in the 1980s in response to rising healthcare expenses. With the goal of enhancing the health of the nation's aging population, the Ministry of Health and Welfare established a regulatory framework to approve certain meals with verified

health benefits [13]. These foods were given a specific seal indicating that they were useful foods derived from animals or plants. The (n-3) fatty acids, which are mostly present in fatty fish like salmon, tuna, mackerel, sardines, and herring, are the most studied class of physiologically active components originating from animal products [14]. Omega-3 carboxylic acid and omega-3 fatty acid are the two major (n-3) carboxylic acids [13]. DHA, an omega-3 fatty acid, maybe a critical component of cellular membrane phospholipids, particularly in the brain and retina of the eye, and is required for optimal function [15]. DHA is critical for the development of these two organs in infants, and the FDA just recently approved the use of DHA and arachidonic acid in infants [16]. Many clinical studies [17, 18] have been carried out to investigate the physiological effects of (n-3) fatty acids in chronic conditions such as cancer, autoimmune disease, psoriasis, Crohn's disease, and cognitive dysfunction (Fig. **1**), with the best-documented health benefit being their role in heart diseases [12, 19].

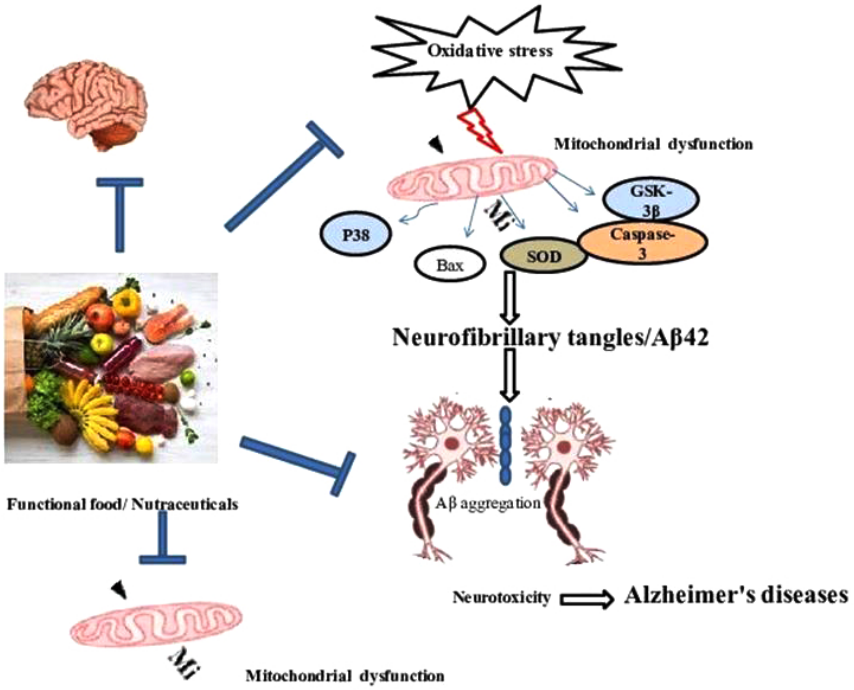

Fig. (1). Schematic diagram showing the role of functional foods in Alzheimer's disease.

The biological effects of the compounds [20] found in food and food-related items may be linked to their affinity for proteins, which is mediated via the inhibition or modification of particular enzymes, as well as their antioxidant activity (Fig. **1**). Furthermore, because of their link to oxidative stress-mediated illnesses, the antioxidant properties of bioactive chemicals from plant diets have been

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

L

M

N

O

P

Q

R

S

T

V

W

X

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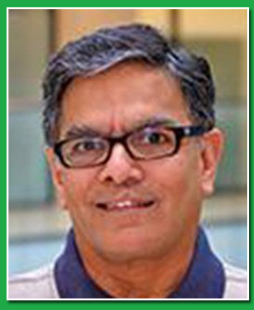

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