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CANCER PREVENTIVE AND THERAPEUTIC COMPOUNDS: GIFT FROM MOTHER NATURE

Editors:
Sahdeo Prasad
Amit Kumar Tyagi

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Cancer Preventive and Therapeutic Compounds: Gift From Mother Nature

Edited by

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CONTENTS

FOREWORD i

PREFACE iii

LIST OF CONTRIBUTORS iv

CHAPTER 1 DIETARY AGENTS: EFFECTIVE AND SAFE NATURAL ASSETS AGAINST CANCER 3

Sahdeo Prasad and *Amit K. Tyagi*

INTRODUCTION 3

FRUITS AND VEGETABLES 5

LEGUMES 8

GRAINS AND CEREALS 9

NUTS 11

SPICES 12

CONCLUSION 13

CONFLICT OF INTEREST 14

ACKNOWLEDGEMENTS 14

REFERENCES 14

CHAPTER 2 MEDICINAL IMPORTANCE OF ALLICIN – A BIOACTIVE COMPONENT FROM ALLIUM SATIVUM L (GARLIC) 20

R. Jayaraj and *Roshan Lal*

INTRODUCTION 20

Chemistry, Biosynthesis and Degradation 21

Medicinal Importance 23

CONCLUDING REMARKS 26

CONFLICT OF INTEREST 26

ACKNOWLEDGEMENTS 26

REFERENCES 27

CHAPTER 3 BOSWELLIC ACIDS AS POTENTIAL CANCER THERAPEUTICS 32

Manjeet Kumar, Arvind Kumar, Omkar P. Dhamale and *Bhahwal Ali Shah*

INTRODUCTION 32

History and Background 33

Botanical and Geographical Distribution 34

Boswellic Acids: 35

Biological Studies 38

Topoisomerase Inhibitors 38

NF-κB Signalling 40

Caspase Activation 41

PI3/AKT Kinase Inhibitors 41

Other Targets 42

Structure Activity Relationship 43

CONCLUSION 54

CONFLICT OF INTEREST 54

ACKNOWLEDGEMENTS 54

REFERENCES 54

CHAPTER 4 NATURAL COMPOUNDS: CANCER PREVENTIVE AGENTS 64

Sandeep K Misra

INTRODUCTION 64

CANCER PREVENTION THROUGH NATURAL SOURCES 65

Curcumin 65

Tea Polyphenols 66

Resveratrol 68
Lycopene 69
Pomegranate 70
Luteolin 71
Genistein 72
Mushrooms 73
Sulforaphane 73
Ginseng 74
Flaxseed 75
Other Promising Natural Agents 75
MOLECULAR TARGETS FOR NATURAL CHEMOPREVENTIVE AGENTS 76
p53 Family Members 76
Activator Protein 1 77
Nuclear Factor-Kappa B 77
Growth Factors and Their Receptors 78
Signal Transducers and Transcriptional Activators 79
Immunoprevention 79
CONCLUDING REMARKS 80
CONFLICT OF INTEREST 82
ACKNOWLEDGEMENTS 82
REFERENCES 82

CHAPTER 5 AFRICAN MEDICINAL PLANTS: AN UNTAPPED RESERVOIR OF POTENTIAL ANTICANCER AGENTS 87
Conrad V. Simoben and *Fidele Ntie-Kang*
INTRODUCTION 87
Cancer in Africa 87
Current Clinical Management of Cancer 88
Africans and the Use of Natural Products for Cancer Chemotherapy 88
SOME ISOLATED COMPOUNDS FROM AFRICAN MEDICINAL PLANTS WITH MEASURED ANTICANCER ACTIVITY 89
Alkaloids 90
Flavonoids 91
Quinones 92
Diterpenoids and Triterpenoids 93
Xanthones 94
Other Compound Classes 95
CONCLUSION 98
CONFLICT OF INTEREST 99
ACKNOWLEDGEMENTS 99
REFERENCES 99

CHAPTER 6 PHYTOCHEMICALS IN THERAPY OF RADIATION INDUCED DAMAGE AND CANCER 105
Pankaj Taneja, Mehak Gulzar, Neetu Kumra Taneja, BS Dwarakanath and *RP Tripathi*
INTRODUCTION 105
Amaranthus Paniculatus 107
Bael (Aegle Marmelos) 108
Angelica Sinensis 108
H. Rhamnoides 109
Holoil 109
Ginseng 110
Moringa Oleifera 111
Biophytum Sensitivum 111
Acanthopanax Senticosus 112
Aloe Vera; Barbadensis 112
Mentha 113
Coronopus Didymus 113

Centella Asiatica 113
Glycyrrhiza Glabra 114
Tephrosia Purpurea 114
Emblica Officinalis 115
Clinical Trials 115
CONCLUSION 116
CONFLICT OF INTEREST 116
ACKNOWLEDGEMENT 116
REFERENCES 117

CHAPTER 7 MARINE NATURAL PRODUCTS FOR CANCER PREVENTION AND THERAPY: A MECHANISTIC OVERVIEW 125
Shankar Suman, Sanjay Mishra and *Yogeshwer Shukla*
INTRODUCTION 125
How Cancer Preventive or Therapeutic Agents Alter Carcinogenesis? 126
Targeting Cancer Associated Signaling Pathways 127
Targeting Drug Resistance Transporter Proteins 128
Inducing Cell Cycle Arrest, Cell Death and Immunomodulation 129
Target Different Cellular Machinery to Suppress Tumor Development 130
Major Biological Resources of Cancer Preventive Natural Marine Products 130
Anti-Cancer Activities of Marine Flora 133
Marine Micro-flora 133
Algae 133
Marine Flowering and Coastal Plants 134
Anticancer Activities of Marine Fauna 134
Porifera 135
Cnideria 135
Arthropoda 137
Bryozoa 137
Mollusca 137
Chordata 138
Marine Products as Nutraceuticals with Cancer Chemoprevention Potential 139
SCOPE, SUMMARY AND CONCLUDING REMARKS 139
CONFLICT OF INTEREST 140
ACKNOWLEDGEMENTS 140
REFERENCES 140

CHAPTER 8 NATURAL PRODUCTS AS A UNIQUE SOURCE OF ANTI-CANCER AGENTS 147
Shinjini Singh
INTRODUCTION 147
TREATMENT MODALITIES OF CANCER 148
HISTORY OF NATURAL COMPOUNDS AS CANCER THERAPEUTICS 150
ROLE OF MARINE NATURAL COMPOUNDS AND THEIR DERIVATIVES IN CANCER PREVENTION 154
Alkaloids 154
Amine Derivatives 154
Macrolides 155
Peptides and Polypeptides 155
Phenols/Polyphenols 156
Polysaccharides 156
Quinones 156
Sterols and Steroids 157
Terpenes 157
ROLE OF NATURAL COMPOUNDS FROM PLANTS IN CANCER PREVENTION 158
Taxanes 158
Vinca alkaloids 159
Camptothecins 159
Epipodophyllotoxins 159
Curcumin 160

Punica Granatum 161
Myrrh 162
Green Tea 163
ROLE OF NATURAL COMPOUNDS FROM MICROBIAL SOURCES IN CANCER PREVENTION 164
ROLE OF NUTRACEUTICALS IN THE PREVENTION OF CANCER 166
ROLE OF FUNCTIONAL FOODS IN THE PREVENTION OF CANCER 166
CONCLUSION 167
CONFLICT OF INTEREST 168
ACKNOWLEDGEMENTS 168
REFERENCES 168

CHAPTER 9 TRANSLATION OF NATURAL PRODUCTS INTO CLINICALLY EFFECTIVE DRUGS: HOW FAR WE HAVE GONE 182
Ammad Ahmad Farooqi, Ilhan Yaylim, Rukset Attar, Muhammad Zahid Qureshi, Faiza Yasmeen and *Sobia Tabassum*
INTRODUCTION 183
PROSTATE CANCER 183
COLORECTAL CANCER 185
LUNG CANCER 185
HEPATOCELLULAR CARCINOMA 186
PANCREATIC CANCER 186
NATURAL PRODUCT INDUCED MODULATION OF EPIGENETIC MACHINERY 187
Ongoing Trials 187
CONCLUSION 189
CONFLICT OF INTEREST 190
ACKNOWLEDGEMENTS 190
REFERENCES 190

SUBJECT INDEX 194

FOREWORD

Among various chronic diseases, cancer is one of the most dreaded diseases throughout the world. Despite dramatic improvements in surgical and reconstructive techniques, the overall mortality rates for cancer remain relatively unchanged. To date, numerous screening and preventive approaches have been directed towards cancer, which clearly reflect a decrease in the morbidity and mortality associated with cancer. The screening measures include physical exam and history, laboratory tests, imaging and genetic tests on timely basis. However, primary prevention of cancer is more important to keep cancer away from developing. This includes maintaining a healthy lifestyle and avoiding exposure to known cancer-causing substances. Thus cancer risk can be reduced with healthy choices like avoiding tobacco, limiting alcohol use, protecting skin from the sun and avoiding indoor tanning, eating a diet rich in fruits and vegetables, keeping a healthy weight, and being physically active.

Lifestyle plays an important role in the prevention of this disease. By adopting a diet consisting primarily of whole grains, fruits and vegetables with limited amounts of meat, primarily chicken or cold-water fish, and doing daily exercise, several risk factors can be avoided. Various methods are available for the treatment of cancers and the selection will depend on the cost, morbidity, requirement of reliable biopsy specimens, resources available, etc. Thus management of cancer by self-care could be a great potential to improve detection and the treatment of cancer; morbidity and mortality also will decrease as a result. The field has broad and wide applications and with every new development reported in leading peer-reviewed journals across the globe, the opportunities only become wider and the hopes brighter.

The editors Dr. Sahdeo Prasad and Dr. Amit Tyagi have done an excellent job of bringing out timely peer-reviewed chapters under the banner "*Cancer Preventive and Therapeutic Compounds: Gift From Mother Nature*" with contributors spreading across four different continents. I complement the authors and appreciate their efforts in bringing out this comprehensive compilation. It is quite impressive to note that the editors have tried to capture such a wide and dynamic topic in a series of attractive articles highlighting different forms of cancer prevention and treatment research, both existing and newly emerging technologies in the field, approaches, advantages, thoughts from around the world along with potential future prospects. The simplicity of the language and presentation style is very much appealing and impressive.

It is my great pleasure to pen down/write the foreword for this prestigious, multi-authored book compilation withpeer-reviewed chapters. This book will be a valuable resource for the scientists and students seeking updated and critical information for their experimental plans. It will be very useful for the clinician to develop clinical trials using natural compounds with or without existing therapeutic drugs. Pharmaceutical companies could design new formulations based on the literature available in this new book. Most importantly, normal population and cancer patients can be benefited by knowing the preventive and therapeutic efficacy of natural

compounds. They can use these natural compounds in their routine life. This book could be a major breakthrough worldwide for the readers, particularly the cancer patients.

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PREFACE

Cancer is one of the leading causes of deaths around the world and it is globally increasing. The highest incidence rates are in the developed countries such as the USA, and the lowest rates are found in developing countries. These differences in incidence rates appear to be attributable to geographical differences in diet and environmental exposure. Although environmental and genetic factors are the major risk factors for cancer, lifestyle also contributes to the development of this disease. Although screening modalities for early detection and therapeutic management of cancer have improved considerably, this disease still needs better treatment modalities. Since long-term use of cytotoxic chemotherapy and radiotherapy can have severe side effects and since tumors can develop resistance to these therapies, agents that can overcome tumor resistance, enhance the therapeutic efficacy of existing drugs and can control multiple signaling pathways are needed to treat cancer.

Although numerous anticancer drugs are available, most of them are expensive and have serious side effects. Thus, the challenging task of finding an alternative cancer treatment measure has become more important than ever to both scientists and physicians. Since natural compounds have been identified and explored for their health benefits for centuries, several nutritional factors have attracted considerable attention as modifiable risk factors in the prevention and treatment of cancer. Natural products are important sources of anti-cancer lead molecules; even many successful anti-cancer drugs approved by FDA are natural products or their derivatives. Still many more are under clinical trials. Based on the current available research, the present book will focus on the chemopreventive and anti-cancer activities of different natural/dietary compounds such as fruits, vegetable, spices, legumes, nuts, grains, and cereals highlighting their potential use against cancer treatment. Since these natural compounds including fruits and vegetables contain a wide variety of phytochemicals, they may have anti-carcinogenic effects. Evidences showed that the phytochemicals present in fruits and vegetables modulate large numbers of cell signaling molecules linked with cancer. The modulation of signaling molecules controls the abnormal growth of cells and ultimately controls the growth of cancer. Also antioxidative and anti-inflammatory properties of natural compounds could hold promise for cancer chemoprevention because oxidative stress and chronic inflammation play important roles in cancer development.

This book is the culmination of the efforts of several researchers, scientists, graduate students and post-doctoral fellows across the world. In this book authors focused on the role of natural compounds in the prevention and therapy of various cancers. The book has enormous scope and will benefit multiple audience including researchers, clinicians, patients, academicians, industrialists, and students. The editors are also thankful to Bentham Publisher and their team members for the opportunity to publish this book. Lastly we thank our family members for their love, support, encouragement and patience during the entire period of this work.

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CHAPTER 1

Dietary Agents: Effective and Safe Natural Assets Against Cancer

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Abstract: Cancer stands as the second most common cause of disease-related death in humans. Although numerous anticancer drugs are available, mostly they are expensive with serious side effects. Thus, the challenging task of finding an alternative cancer treatment measure has become more important than ever to both scientists and physicians. Since natural compounds are known for their various health benefits for centuries, several nutritional factors have brought considerable attention as modifiable risk factors in the prevention and treatment of cancer. Based on currently available research, the present chapter focuses on the chemo preventive and chemotherapeutic properties of different natural/dietary compounds such as fruits, vegetable, spices, nuts, legumes, cereals and grains highlighting their potential use against cancer treatment. The molecular mechanisms by which theses dietary compounds inhibit cancer development and induce cell death are also included to a certain extent.

Keywords: Cell signaling molecules, Cancer, Chemoprevention and chemotherapy, Inflammation, Natural compounds.

INTRODUCTION

Cancer is one of the major health problems not only in the United States, but also in many other countries of the world. At present, 1 in 3 women and 1 in 2 men in the USA will develop cancer in their lifespan [1]. Although radiation-therapy, surgery and chemotherapy are the standard ways to treat most kinds of cancers, reoccurrence of cancer and resistance to chemotherapeutic drugs have become major impediments for treating cancer. Moreover, multidrug resistance of cancer is now considered a main reason for the failure of chemotherapy [2]. Alternatives

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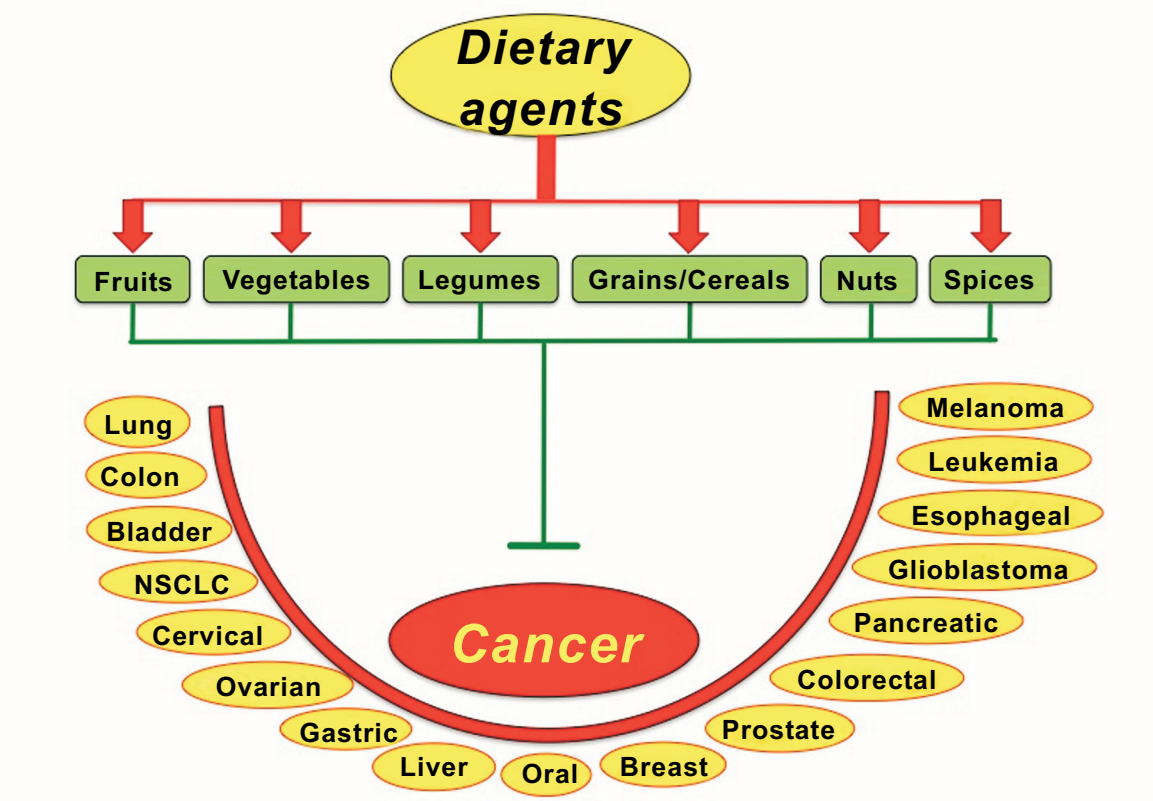
that are inexpensive, effective, and safe compared with synthetic chemo-therapeutic agents are profoundly required. An abundance of epidemiological, clinical and experimental evidences have shown that use of the compounds from natural sources play an important preventive and therapeutic role in the etiology of human cancers (Fig. **1**).



various diseases including cancer. Many drugs against cancer approved by FDA are originated from natural products or their derivatives. Still several natural compounds are under clinical trials. These natural products include fruits, vegetables, legumes, cereals, and nuts, which are being routinely consumed by human (Fig. **2**). The anticancer compounds are usually present in any part of the plant such as roots, leaf, bark, flower, fruits etc. Accumulated data from preclinical and clinical studies revealed that these natural compounds are chemically diverse because they can act at several stages of tumor development. In this chapter we discuss some selected type of cancer preventive and therapeutic compounds provided by Mother Nature.

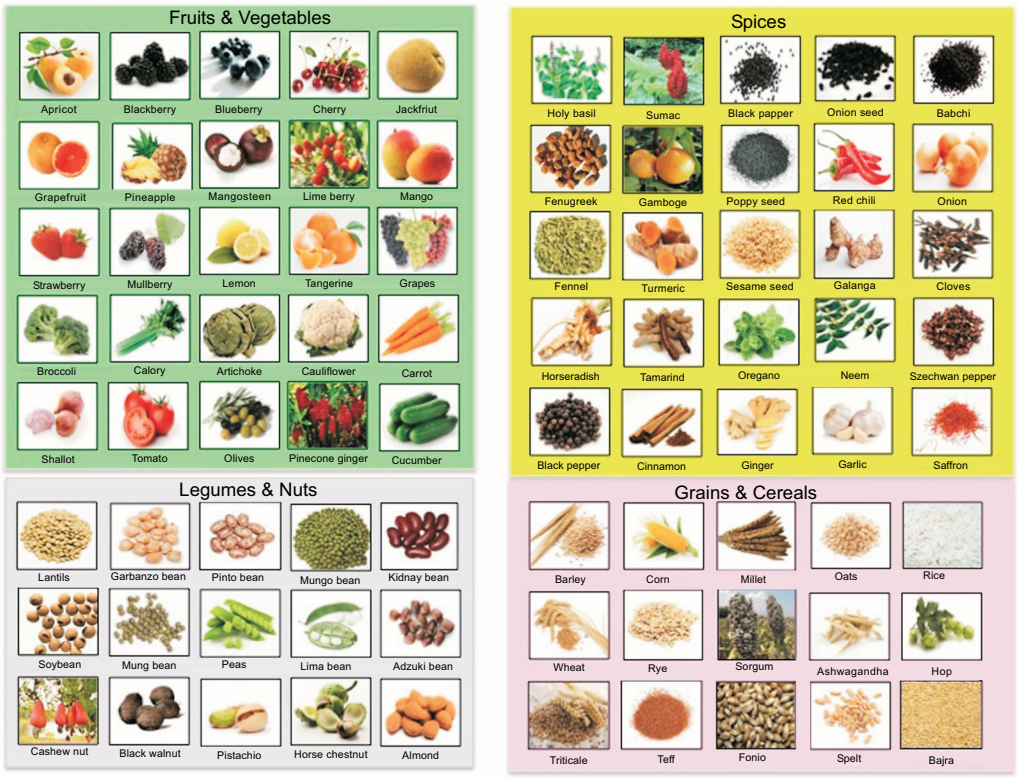


Fig. (2). Selected cancer preventive and therapeutic compounds provided by Mother Nature.

FRUITS AND VEGETABLES

Varieties of phytochemicals are reported to found in fruits and vegetables, which could have potential against the cancer. These phytochemicals have antioxidant and anti-inflammatory activities, which contribute to the prevention of tumorigenesis. Because chronic inflammation and oxidative stress are associated with the development of cancer, fruits and vegetables with these properties hold promise for cancer chemoprevention. These phytochemicals in fruits and vegetables can help prevent cancer [3]. The phytochemicals present in fruits and vegetables modulate large number of cell signaling molecules those linked with cancer. The modulation of signaling molecules controls the abnormal growth of cells and ultimately controls the growth of cancer.

A large number of laboratory studies have revealed that phytochemicals from fruits and vegetables inhibit every step of cancer development and thus display chemo preventive and chemotherapeutic potential against cancer cells. These phytochemicals exhibit anticancer activity against varieties of cancers including lung carcinoma, oral cancer, leukemia, breast cancer, multiple myeloma, head and

CHAPTER 2

Medicinal Importance of Allicin – A Bioactive Component from *Allium Sativum* L (Garlic)

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Abstract: *Allium sativum* L (garlic) has a lengthy history as being a food and spice having a unique taste and odor along with many medicinal properties. Garlic is considered to be a natural medicine against variety of human ailments, including various antibacterial, antiviral and antifungal infections, antithrombotic, anticancer and anti tumorogenic activities. All these activities are linked to the level of organosulfur compounds like allicin, flavonoids, and phenolic components in it. Freshly chopped garlic contains Allicin, which is one of the highly biologically dynamic component. Allicin has reported to have a number of bioactivities including antioxidant, anti-inflammatory activities. Many cardiovascular activities of allicin also have been worked out. The present paper reviews one of the major active ingredients in garlic – allicin – for its medicinal importance.

Keywords: Allicin, *Allium sativum*, Anti-cancer activities, Molecular targets.

INTRODUCTION

Dietary garlic is reported to have a number of health effects and is utilized over centuries for protection against microbial infections, chronic health effects and cancer. The medicinal properties of garlic (*Allium sativum*) has been known to mankind over thousands of years. The olden literatures and folklores of Egyptians, Indians, Romans, Babylonians and Greeks has mentioned the frequent use of garlic for various ailments such as respiratory infections, intestinal disorders, skin diseases, flatulence, worms, wounds, symptoms of aging are few among others [1].

The wound healing properties of garlic has been used by soldiers during World War II [2]. The spread of infections in wounds were inhibited through the

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Sahdeo Prasad & Amit Kumar Tyagi (Eds.)

application of garlic paste directly to wounds. In addition to this, garlic displays a number of bioactivities such as procirculatory effects, hypolipidemic, and antiplatelet activities. The immune enhancement property of garlic is found to preclude flu and cold symptoms and also exhibits chemo preventive and anticancer activities, enhanced xenobiotic effects, regaining of physical fitness, radioprotection, anti-aging effects and stress reducing effects. Clinical and experimental studies on the intake of garlic preparations especially of garlic extract have shown widespread biological activities [3]. The garlic extracts reported to have hepatoprotective, neuroprotective, and antioxidative activities [4]. The *in vitro* activity of garlic against *Mycobacterium tuberculosis* has been reported long ago [5]. The cholesterol lowering effects of garlic supplements in humans were established in several clinical studies [6, 7]. According to the Ayurvedic and Greek systems of medicine, garlic is established as one of the best remedies for treatment of tuberculosis [8]. Many recent studies established that, consumption of allium-containing diet, lowered the threat of developing numerous malignancies [9 - 12], however the underlying signal transduction mechanisms were yet to be identified.

Both freshly chopped and crushed garlic is abundant with a group of organosulfur compounds called thiosulfinates, which are considered to be the reason for the beneficial effects. Garlic socked with warm oil contained mainly vinyldithiins, ajoene and small amount of sulfides [13, 14]. Freshly crushed garlic contains numerous sulfur compounds together labelled as garlic organosulfur compounds, which are the primary chemical entities accountable for the bioactivity of garlic. The major organosulfur chemical in garlic is (+) S-allyl-L-cysteinesulfoxide (alliin) that is normally stored away from the enzyme alliinase (EC 4.4.1.3). On crushing or chewing garlic, alliinase interacts with its substrate alliin to form 2-propenesulfenic acid, and on condensation it forms diallylthiosulfinate (allicin) [15]. Commercially obtainable garlic supplements are characterized into; garlic oil, dehydrated garlic powder, aged garlic extract (AGE) and garlic oil macerate.

Allicin - diallylthiosulfinate is one of the key bioactive compounds of garlic first isolated in 1944 and reported to have antifungal and antibacterial properties [16]. Allicin is reported to have enormous spectrum of health beneficial effects including: antihypertensive, cardioprotective, antimicrobial, antifungal, cardioprotective, antiparasitic, anticancer and antiinflammatory activities [17 - 20].

Chemistry, Biosynthesis and Degradation

Allicin is chemically diallylthiosulfinate (IUPAC name: 3-prop-2-enylsulfinylsul-

fanylprop-1-ene) with a molecular formula $C_6H_{10}OS_2$ and molecular weight - 162.273 g/mol. Garlic (*Allium sativum*) is the natural source of allicin and garlic is being used as a food ingredient as well as in folk medicine across many civilization around the world since centuries. The defense mechanism of garlic against attacks by pests is through allicin. When the garlic plant is injured or attacked, it produces allicin by an enzymatic reaction and allicin is toxic to insects and microorganisms. The aroma of the freshly chopped garlic is also due to the presence of allicin [21]. Allicin is highly unstable and rapidly changes into a series of other sulfur containing compounds such as diallyl disulfide [22].

The enzyme alliinase acts on alliin (S-allyl-Lcysteine sulfoxide) forms allicin, which is present in the racemic form. Oxidation of diallyl disulfide also lead to the generation of racemic form of alliin [23]. In garlic cloves, alliin and alliinase are stored in different compartments, upon crushing of the cloves, both interact to form allicin, pyruvic acid and ammonia. Allylsulfenic acid is highly unstable and very reactive at room temperature. With the elimination of water, two molecules of allylsulfenic acid condense spontaneously to form allicin (Fig. **1**).

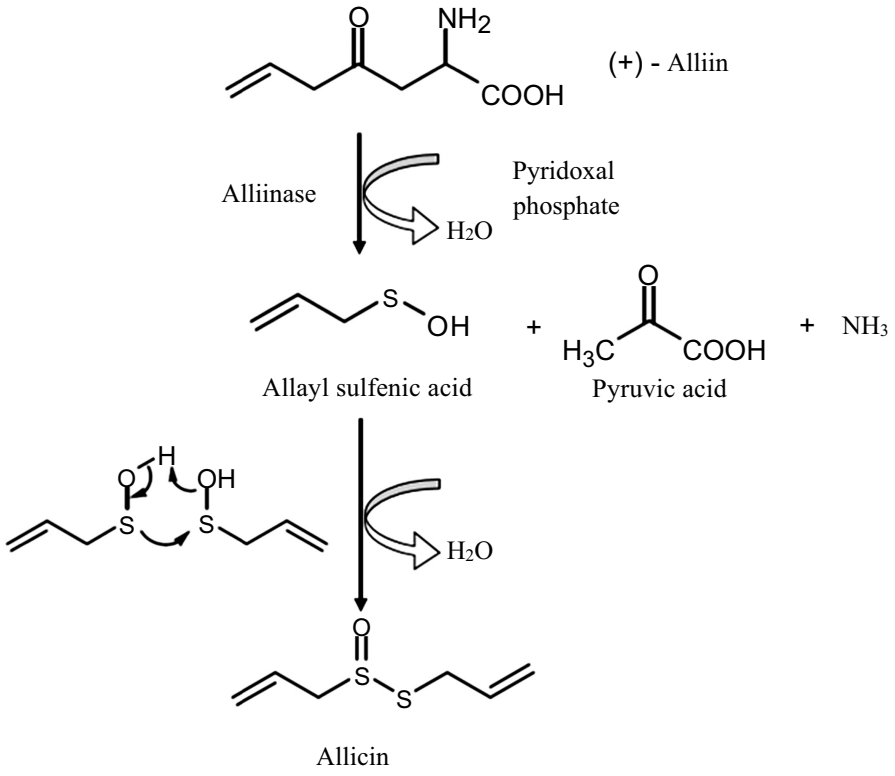

Fig. (1). Scheme of allicin biosynthesis.

CHAPTER 3

Boswellic Acids as Potential Cancer Therapeutics

Manjeet Kumar[1], Arvind Kumar[1], Omkar P. Dhamale[2] and **Bhahwal Ali Shah[1,*]**

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Abstract: Cancer is the second leading cause of deaths worldwide, while it finds the top spot in diseases which still are not 100% curable. In the past few decades, a great deal of progress has been made in discovering new chemical entities, which enables us to understand the cause of cancer at cellular and molecular levels. In this regard, one of the naturally occurring triterpenoid class of compounds known as boswellic acids (BAs), have shown great potential for the development of new anticancer drugs. The interest in these type of triterpenoids has augmented since molecules such as NVX-207 and CDDO-Me have reached clinical trials. The alcoholic extract of the gum has also undergone clinical trials for the treatment of endotoxin induced hepatitis. Recently, the use of boswellic acid as well as its semi synthetic derivatives to treat cancer had been considered as an emerging concept in oncology as these have garnered considerable attention as a chemo-preventive and therapeutic agent in cancer.

Keywords: Anti-cancer, *Boswellia* sp., Boswellic acids, Pentacyclic triterpenes.

INTRODUCTION

Boswellic acids (BAs), pentacyclic triterpenoid class of natural products are widely known for their anti-inflammatory and anti-arthritic activities [1 - 3]. They inhibit 5-lipoxygenase, an enzyme that produces leukotriene, which is mainly responsible for the body inflammation and interfere with many other biological pathways. These complex scaffolds are generally available from natural sources and because of the numerous stereogenic centers in the aliphatic cyclic systems, their total synthesis and derivatization is relatively more challenging. This class of compounds has provided promising leads for the development of new anti-cancer drugs [4]. The interest for these types of pentacyclic triterpenoids has also grown

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Sahdeo Prasad & Amit Kumar Tyagi (Eds.)

since the clinical trials for NVX-207 (**1,** GZ 68·205/53-BrGT/2007) and CDDO-Me (**2,** https://clinicaltrials.gov/ct2/results?term=CDDO+methyl+ester&Search=Search) for cancer treatment (Fig. **1**) [5, 6].

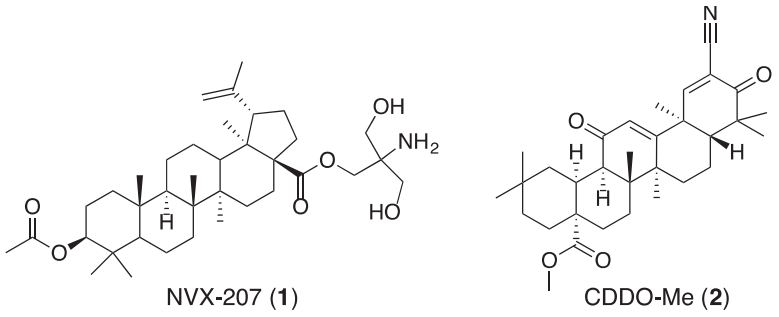

Fig. (1). Triterpenoids under clinical evaluation.

In the recent past, several reviews have been published, highlighting the chemistry and biology of BAs, which can be consulted for more details in their respective areas [1 - 3, 7 - 11]. This chapter serves as a summary of isolation, characterization, and biological scope focused on anti-cancer studies and recent structure-activity relationships of newly developed BAs analogues.

History and Background

BAs are the important constituents of *Boswellia* genus, which contain almost 25 species, widely distributed in the dry areas of the Horn of Africa, the Arabian Peninsula and in India (Table **1**) [12 - 19]. Of all, *B. Serrata* is one of the most attractive and highly investigated species, generally found in subcontinent of India (Western Himalayas, dry hill forests of Rajasthan, Gujarat, Maharashtra, Madhya Pradesh, Bihar, Orissa). It belongs to the Burseraceae family, commonly known as frankincense, shallaki, salai guggal, white guggal, Indian olibanum or dhup, having a long history of use as incense in religious and cultural ceremonies [20]. In addition to this, there are written evidences where frankincense had been documented as drug in various diseases [21 - 34]. Probably, the oldest pharmacological note, the papyrus Ebers (received by a Professor of Egyptology, Moritz Fritz Ebers in 1873 from an Arabian businessman, found in between the legs of a mummy of Luxor), quoted about 900 medical prescription regarding the practical information of diagnosis and treatment of internal diseases, had also mentioned frankincense as a drug used for treatment of various diseases. The age of the Papyrus Ebers is dated to the time of Pharaoh Amenophis I and was most likely written around 1500 BC [35]. The use of the oleogum resin of *B. serrata* is also

described in Ayurvedic text books (Charaka Samhita, 1st 2nd century AD and in Astangahrdaya Samhita, 7th century AD). Medical preparations containing the bark or the oleogum resin of *B. serrata* were used to treat a variety of diseases including tumors, carcinomas and oedemas. Moreover, respiratory tract like cough, other respiratory problems as well as diarrhoea, constipation, flatulence and central nervous diseases were also treated.

Table 1. Some of the important *Boswellia* species and their geographical distribution.

Species	Geographical Distribution
B. ovalifoliolata Bal. & Henry	India
B. pirottae Chiov.	Ethopia
B. neglecta S. Moore	Somalia, Kenya
B. dalzielii Hutch.	Tropical Africa
B. papyrifera Hochst.	Ethiopia, Eritrea, Sudan
B. rivae Engl.	Ethopia
B. hildebrandtii Engl.	Somalia
B. ogadensis Vollesen	Ethopia
B. popoviana Hepper	Yemen
B. nana Hepper	Yemen
B. dioscorides Thul. & Gifri	Yemen
B. bullata Thul. & Gifri	Yemen
Boswellia carterii Birdw.	Somali, Nubia
Boswellia sacra Flück.	Oman, Yemen
Boswellia frereana Birdw.	Somalia
Boswellia odorata Hutch.	Tropical Africa
Boswellia ameero Balf. Fils.	Yemen, Socotra
Boswellia elongata Balf. Fils.	Yemen, Socotra
Boswellia socotrana Balf. Fils.	Socotra
Boswellia serrata Roxb.	India

Botanical and Geographical Distribution

Boswellia resins are harvested during the start of hotter period of the year. After a certain time the deciduous tree exude viscous liquid, which on air exposure transforms into a solid gum resin. Depending upon the age, height and condition of tree, its exploitation is executed for three consecutive years and yields about 3-10 kg of oleo-gum resin [36]. More than 200 compounds have been isolated from the oleogum resin of different Boswellia species including polysaccharides,

CHAPTER 4

Natural Compounds: Cancer Preventive Agents

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Abstract: Cancer chemoprevention is a rapidly evolving scientific research area. Cancer chemoprevention is the application of natural or synthetic agents to reduce or delay the onset of cancer. Different approaches are currently being used for cancer prevention and one of these important approaches is the use of natural compounds. Several natural compounds are currently under the investigation for their efficacy in preventing cancer. These compounds include curcumin, tea polyphenols, resveratrol, genistein, luteolin, lycopene among others. Curcumin is probably the most studied natural molecule for its ability to prevent cancer. Many of these compounds are being investigated using *in vitro* as well as animal models. Clinical trials are also underway for many natural compounds to test their efficiency in cancer chemoprevention. Recent evidence suggests that these natural molecules have antioxidant, anti-inflammatory, immune-enhancing, cell cycle modifying and cell differentiating, apoptotic and suppression of proliferation and angiogenesis properties. These natural compounds target several molecular pathways. Some of these pathways include p53 family, activator protein 1, NF-κB, growth factors among others.

Keywords: Cancer chemoprevention, Molecular pathways, Natural compounds.

INTRODUCTION

The cancer is the second leading cause of death in the USA [1]. Cancer patients apply all the possible efforts to fight the disease, and manage its symptoms. However, numerous side effects have been found to be associated with currently available treatment regimens. Thus, it's better to prevent the disease than to treat it. Several approaches are suggested that may prevent the onset of cancer. These approaches include changes in the dietary intake, taking nutritional supplements, lifestyle modifications, like exercise and reducing exposure to the sun and decreasing exposure to the polluted environment [2].

Cancer chemoprevention is a way to prevent cancer from originating, or slow

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down the progression, or reverse the cancer disease by the administration of one or combination of a few natural and/or synthetic chemical agents.

Research on cancer prevention is an emerging field now and there is not a lot of information available for the ways to prevent the onset of cancer. Theories of cancer prevention generally originate from correlations, observation of populations, and lifestyle as well as diet patterns at the national or cultural level. These factors may affect the rate of onset of cancer. More and more people in the USA and worldwide are leaning towards the complementary and alternative medicine for preventing and managing the disease. An important category in this group is the use of the natural compounds that prevent and treat cancer. Avoidance of chemical, biologic, and physical agents that cause cancer and the eating diets high in cancer preventive factors is the two most important approaches for cancer prevention. It is estimated that just by modification of diet alone, for *e.g.*, increasing high intake of fruits and vegetables, one can reduce the cancer occurrence by 20%.

CANCER PREVENTION THROUGH NATURAL SOURCES

Cancer preventive agents may include foods, spices, compounds extracted from the plants, or specific nutrients found in nature. Cancer prevention research that employs natural compounds are often studied for their role in specific physiological pathways. Most of the published literature on food chemoprevention focuses on changing the nutrition behavior. These include increasing the intake of fruits, vegetables, and foods made from whole grains. These chemopreventive agents may have various properties that make them suitable candidates. Most of these agents have antioxidant and apoptotic, antimetastatic activities and are able to modulate the immune system and hormones. Some of these candidates that have shown their role in cancer prevention are summarized here.

Curcumin

Curcumin is an extract of the rhizome of the turmeric plant (*Curcuma longa*) and it is a major yellow pigment of turmeric. It is the main curcuminoid of turmeric and exhibit potent antioxidant and anti-inflammatory effects. The curcuminoids are natural phenols that impart the yellow color to turmeric. Curcumin may exist in 1,3-diketo and equivalent enol tautomeric forms, (Fig. **1**). The enol form is more energetically stable in the solid phase and in organic solvents, and the 1,3-diketo form is predominantly present in the water.

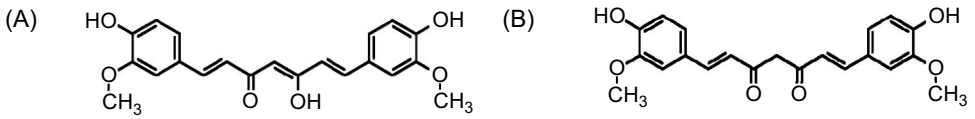

Fig. (1). Structure of curcumin (A) Enol form (B) Keto form.

Turmeric and its extract have been used traditionally as medicine for centuries in treating various symptoms. However, much attention has been paid only recently, for its anticancer activity. Probably, it is the most widely studied natural chemopreventive agent for many cancers, including breast, cervical, colon, gastric, hepatic, leukemia, oral epithelial and ovarian cancer. The role of curcumin in biochemical pathways has been studied in detail. Curcumin targets multiple molecules- that include Ap-1, NF-κB, Akt, STAT3, Bcl-2, Bcl-XL, Poly (ADPribose) polymerase, caspases, Ikappa B kinase, human epidermal growth factor receptor 2, epidermal growth factor receptor, Jun N-terminal Kinase, cyclooxygenase 2, mitogen-activated protein kinases, and 5-lipoxygenase. Curcumin has been reported to induce phase II enzymes, like glutathione S-transferase, as well as inhibit phase I enzymes. Curcumin has been studied in detail in colon cancer models. It has been shown to interrupt the process of carcinogenesis by inhibiting the initiation step or suppressing the promotion and progression steps in the animal models [3, 4]. Curcumin also inhibited the growth of cancer cells *in vitro* and in xenograft models by inducing cell cycle arrest and apoptosis [5 - 7]. Besides these, curcumin also exhibits synergistic che-mopreventive effects with polyphenols found in food, like, genistein [8], green tea [9] and embelin [10]. The activity of several drugs to treat cancer, like, vinorelbine, vinca alkaloid, and fluorouracil is enhanced by the curcumin. More than five phase I clinical trials have been completed for curcumin and establish its tolerability and the safety in patients with colorectal cancer. In these study, up to eight grams curcumin was administered per day [11]. The side effects were very mild and only a few subjects reported mild nausea and diarrhea.

Tea Polyphenols

Tea is the most widely consumed beverages in the world except water. It is the only beverage that is served hot or iced, anytime, anywhere for any occasion. The tea is rich in chemicals that have strong antioxidant activities. Several epidemiological studies from around the world, including *in-vivo* models, indicate that green tea reduces the onset of cancer. Different types are tea are obtained based on processing techniques, including green and black tea. Both these tea types have been investigated for their effectiveness in preventing cancer. Green

CHAPTER 5

African Medicinal Plants: An Untapped Reservoir of Potential Anticancer Agents

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Abstract: Despite continuing scientific and commercial interests in cancer research around drug discovery, both less developed and developed countries are still trapped in the grip of this deadly and dreadful disease. Naturally occurring compounds represent approximately 50% of the chemotherapeutic agents, which have so far been brought to the market for cancer treatment. Traditional preparations have been the major source of cancer treatment in Africa, with traditional healers making regular use of these plants for the treatment of cancer and other ailments, since the continent is endowed with a rich floral bio-diversity. Africa's medicinal plants are known to biosynthesize interesting chemical structures with promising biological activities Thus, natural products from the African continent hold a premise for drug discovery and it is expected that the next generation of drugs, including potential anti-cancer drugs or the scaffolds necessary for the synthesis of new anti-cancer drugs could be lodged in African plants. We present some promising natural products for the anticancer drug development from African flora.

Keywords: Africa, Cancer, Medicinal plants, Natural products.

INTRODUCTION

Cancer in Africa

Overall, about 847,000 new cancer cases and an estimated 550,000 cancer deaths occurred in Africa in the year 2012 alone [1]; these estimates were expected to double in a few decades because of the adoption of western lifestyles, *e.g.* smoking, poor diet and little physical exercise, along with reproductive factors in economically developing/transitioning countries [2 - 5].

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In spite of this growing burden, cancer continues to receive low public health priority in Africa, mainly due to limited resources and other pressing public health problems, including communicable diseases, *e.g.* the acquired immune deficiency syndrome (AIDS)/human immunodeficiency virus (HIV) infection, malaria and tuberculosis. The three most commonly diagnosed cancers in Africa are lung, stomach and liver in men while breast, cervix uteri and lung are reported for women [2].

Current Clinical Management of Cancer

Cancer is largely feared because it is known to be difficult to cure. Currently there are three major ways of treating cancer: radiotherapy (the use of high-energy radiation to kill/destroy cancer cells), surgery (the removal of infected cells) and the use of cytotoxic drugs (the killing of cancer cells), also known as drug therapy or chemotherapy, each treatment method having significant limitations [6].

Chemotherapy remains one of the main methods of modern cancer treatment by humans [2, 7 - 9]. However, many of these cytotoxic drugs have the potential to be very harmful to the body as they are rarely designed to be "cancer cell-specific" in their modes of action. In addition, adverse and/or side effect(s) resulting from cancer chemotherapy, *e.g.* fatigue, loss of appetite, nausea, vomiting, bowel changes such as diarrhoea, constipation, hair loss, reduced levels of red and white blood cells and platelets, mouth ulcers or mouth infections and skin problems such as itchiness or extreme light sensitivity of the available drugs, cost factors (high cost of the available drugs and the long exposure/treatment period for the disease) also constitute a major limitation [6, 9, 10].

Africans and the Use of Natural Products for Cancer Chemotherapy

The use of plants by humans as medicinal agents (employed as decoctions, concoctions, steam baths, burning of ashes and smearing of liquids and gas upon the patients, among other practices) pre-dates recorded history [11]. The development of formularies and pharmacopoeia from ethno-medical plant use data provides an important solution for global health care, as well as significantly contributing to drug development [12]. It is estimated that 60 – 85% of the world's population especially people living in the rural areas depend directly on plants as medicines for the treatment of various diseases [13 - 16]. Two main reasons lie behind this observation; the low purchasing power within the populations living in the rural areas and the limited access to modern drugs. It is common knowledge that medicinal plants, along with their phytochemicals, have been widely used for their curative purposes. They could therefore be considered

as playing a paramount role as an important source of lead compounds for drug discovery for a variety of diseases [14, 17]. The continent of Africa is very rich in floral biodiversity and the use of these indigenous plants plays an important role in the treatment of several diseases [18, 19]. It is believed that the plant secondary metabolites hold enormous potential for drug discovery [20 - 23]. Reviews that empirically analyze bioactivity, ethnobotanical and ethnopharmacological uses of African plants have also been recently published [18, 24 - 27]. A lot of research efforts on the anticancer activities of plants in Africa used by traditional healers to treat and cure cancer related symptoms have been documented [10, 28 - 31].

SOME ISOLATED COMPOUNDS FROM AFRICAN MEDICINAL PLANTS WITH MEASURED ANTICANCER ACTIVITY

In Africa, traditional healers operate close to the populations, by making use of the biodiversity of plant species in such areas to cure various diseases and ailments. Several steps have been taken towards documenting the ethnobotanical and ethnopharmacological knowledge derived from the use of medicinal plants in Africa. The bioactivities of the metabolites have been recorded [15, 16, 26, 30 - 32]. The anti-cancer properties of some of the compounds identified in the current study have been previously described in some of our reviews [18, 24, 33 - 35]. The following sub-paragraphs discuss some of the isolated metabolites from African flora, along with the most promising compounds and compound classes (summarised in Table **1**).

Table 1. Some selected bioactive compounds from some African medicinal plants with promising anticancer activities.

Isolated metabolites	Plant species (Family)	Part of plant studied	Author, Reference
1-5	*Erythrina abyssinica* (Fabaceae)	Whole plant	Mohammed *et al*. [46]
6-8	*Erythrina excelsa* and *Erythrina senegalensis* (Fabaceae)	Roots	Kuete *et al*. [49]
9-15	*Ardisia kivuensis* (Myrsinaceae)	Stem	Ndontsa *et al*. [50, 51]
		Leaves and stem	
		Leaves and stem bark	Paul *et al*. [52]
16-18	*Albizia grandibracteata* (Fabaceae)	Stem bark	Krief *et al.* [53]
19-22	*Annona senegalensis* (Annonaceae)	Stem bark	Fatope and Audu [54]
23-28	*Allanblackia monticola* (Clusiaceae)	Seeds	Azebaze *et al*. [60]
29-35	*Hypericum riparium* (Guttiferae)	Roots	Tala *et al*. [62]
36 – 41	*Antiaris africana* (Moraceae)	Stem bark	Kuete *et al*. [63]

CHAPTER 6

Phytochemicals in Therapy of Radiation Induced Damage and Cancer

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Abstract: Radiation has been implicated in causing deleterious effect including cancer. Radiation exposure cause mutations, damage to the hematopoietic, gastrointestinal or central nervous systems which are critical causing adverse health effects. Hence, there is an urgent need to prevent such effects. A majority of phytochemicals have potential chemopreventive efficacy with relative less toxicity. Specifically, the utilization of these natural plants as modifiers of the radiation reaction is accepting extensive considerable attention. In this current review, we summarize the antimutagenic and anticancer effects of some selected natural phytochemicals including Amaranthus, Bael, Angelica, Rhamnoides, Haloil, Ginseng, Moringa, Biophytum *etc* against radiation induced damage.

Keywords: Cancer, Phytochemicals, Radiation damage, Therapy.

INTRODUCTION

Radiation harmful reactions of cells are described by damage to biomolecules including DNA lesions, perturbations in cell cycle, cytogenotoxicity, dysregulation of cell signaling and gene expression [1 - 3]. Depending on dose levels and duration of radiation exposure, these can cause mutation, damage to the hematopoietic, gastrointestinal or central nervous systems and cancer [1 - 3].

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We also see that radiation is accounted for therapeutic mortality for the treatment of solid tumors,but its exposure to surrounding normal cells leads to mutation which results in the occurrence of cancer [3, 4]. Moreover, events like the Hiroshoma Nagasaki atomic bomb explosion showed incidences of cancer due to those radiation exposed to populations and to its generations. Hence the radiation protection countermeasures is an urgent need. Using natural products as radioprotectors is of great interest because of their relatively low toxicity and ability to develop better drugs [5, 6]. Focus on plant research has increased in recent times with an aim towards their edible, medicinal and amelioration properties in animal welfare globally. Bunches of proof have gathered to indicate gigantic capability of medicinal nutritional plants in ethical society. In the course of the most recent years, researcher scientists have gone for recognizing, identifying, approving and validating plant inferred substances for disease treatment and combating toxicity. It has been demonstrated that different parts of plants, for example, leaves, organic products, seeds give wellbeing and nourishment in the human diet which has enormous traditional use against various diseases [4 - 6]. These phytochemicals indicate efficient anticancer activity. They have cancer prevention properties with typical features of protecting normal cells from radiation damage. They also exhibit prooxidant function in cancer cells, which increases the damage imposed by radiation [5, 6]. There exists a balance between pro- or antioxidant function of these phytochemicals which is concentration dependent and regulated by cytosolic redox status. The use of these phytochemicals as radio-sensitizing agents is picking up force suggesting it be chemomodulator of radiotherapy making them effective curative agents.We summarize in this review few studies on phytochemicals discussed below for their use as radioprotectors. Most of these herbs are of Indian and Chinese origin because they are one of the most ancient countries using traditional natural products (Text below and Table **1**).

Table 1. Radioprotective effects of few Phytochemicals in cancer.

Phytochemical	Protection	Cancer	Origin
Aegle marmelos Corr.ex.Roxb.	protection against radiation induced sickness, human peripheral blood lymphocytes (HPBLs) irradiated with gamma-radiation	breast cancer	Rutaceae, cultivated in north India
Acanthopanax senticosus	radioprotective effects on hemopoiesis of irradiated mice, Pre-irradiation administration of Shigoka extract (5 mg/kg b.w.; −24 h; i.p.) rendered maximum survival (80%), while post-irradiation administration (+12 h; 9.5 Gy) exhibited 30% survival.	cerebral haemorrhage	Araliaceae

(Table 1) contd.....

Phytochemical	Protection	Cancer	Origin
Amaranthus paniculatus Linn.	Oral administration significant decrease in tumor volume, viable cell count and tumor weight	Ehrlich's ascites carcinoma	Amaranthaceae
Angelica sinensis	effective down-regulation of TNF-· and TGF-ß1 irradiated lung tissue	Lung cancer	Apiacae
Aloe Vera & Aloe barbadenis	contains emodin that activates the macrophages to fight cancer, inhibit metastases	Merkel cell carcinoma	Liliaceae
Biophytum sensitivum	reduce the enhanced level of ALP, GPT and LPO levels and significantly enhance the glutathione (GSH) content in liver and intestinal mucosain gamma irradiated animals,	Liver cancer	Oxidaceae
Centella asiatica	Aqueous extracts protects against low dose ionization radiation, administrative orally total body against sublethal gamma radiation	Whole body	Apiaceae
Coronopus didymus	Optimum radioprotection was observed upon *i.p.* administration, 30 min prior to 10 Gy irradiation	Whole body	Brassicaceae
Emblica officinalis	effectively prevent gamma ray–induced lipid peroxidation	*In vitro*	Euphorbiaceae
Glycyrrhiza glabra	Protection against microsomal membrane gamma radiation induced lipid peroxidation	*In vivo* (rats)	Leguminosae
Hypercium perforatum	Management of acute skin toxicity in head and neck cancer patients undergoing radiation	Head and neck cancer	Hyperiaceae
Hippophae rhamnoides	Dose of 30 mg/kg body weight of RH-3 rendered 82% survival	*In vitro*	Elaegnaceae
Mentha arvensis	Extract provides protection against the radiation-induced sickness and mortality and the optimum protective dose of 10 mg/kg is safe from the point of drug-induced toxicity.	Mice	Laminacaeae
Moringa oleifera	Hepatoprotective effect, pretreatment with MoLE protected against γ-radiation-induced liver damage.	Liver cancer	Moringaceae
Panax ginseng	Protection against gamma radiation, Lipid peroxidation, glutathione,chromosomal damage	*In vivo* / *in vitro*	Aralaceae
Tephrosia purpurea	Tephrosia extract (200 mg/kg b.wt) protected Swiss albino mice against radiation (5 Gy)-induced haemopoietic injury	Mice	Fabaceae

Amaranthus Paniculatus

Amaranthus paniculatus(Amaranthaceae) has Indian name as "Rajgira" and "Amaranth" as English name. It is cultivated as traditional medicinal plant by

CHAPTER 7

Marine Natural Products for Cancer Prevention and Therapy: A Mechanistic Overview

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Abstract: Marine resources have rich pharmaceutical values as they encompass a diverse taxonomy of biological species and possess a large-scale of bioactive compounds. The existence of extraordinary chemical diversity of marine resources is used to discover anticancer agent in its natural or derived synthetic form. Marine flora and fauna possess several valuable compounds with immunostimulatory and antioxidant properties, also gained their importance as nutraceuticals as well as in cancer chemoprevention. In this chapter, we have emphasized for overviewing the marine natural products; those having anticancer or cancer chemo-preventive properties, acting against different deregulated cellular and molecular pathways associated with cancer development or progression.

Keywords: Cancer, Cell signaling pathways, Flora, Fauna, Marine compounds.

INTRODUCTION

Cancer is a global health concern with a high rate of mortality and morbidity. In the recent GLOBOCAN report, 1 million new cases and 8.2 million deaths due to cancer were reported in 2012 [1]. The incidence of cancer has been increasing drastically in the past few decades. Epidemiological studies on cancer showed that various environmental factors and irregular lifestyle are key governing elements of cancer development. Thus, several of naturally available preventive agents are well explored to manage cancer incidence and progression. Marine resources have enormous biological diversity and possess a huge content of bioactive compounds. Hence, there is a growing interest on the screening of marine compounds that possess potent cancer preventive abilities *via* targeting various cellular and molecular machineries associated with cancer. So far, a large-scale

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natural compounds or its derived form of bioactive-compounds are widely studied for their anticancer activities in numerous studies. These compounds have unique abilities to target cell signaling as well as metabolic pathways which are involved in cancer associated cellular processes. Several marine organisms produce a variety of secondary metabolites, which are known for the cancer prevention activity, such as polyphenols, alkaloids, porphyrins, terpenoids, phenazines, fatty acid products, sterols, amino acid analogues, aliphatic cyclic peroxides, peptides *etc*. In the present chapter, several cancer preventive agents are elaborated with their potent targets in cancer-associated pathways, which have a major role in the cancer development and progression.

How Cancer Preventive or Therapeutic Agents Alter Carcinogenesis?

In the last few decades, multiple views from the investigations have delineated the mechanistic pathways in the carcinogenesis. The present conception of neoplastic transformations is the DNA damage and accumulating mutations at genomic level are one of the key factors of the carcinogenic process and these are highly integrated with various types of cellular stresses. Several factors, including hectic lifestyle and environmental toxicants generated cellular stress in the oxidative forms by the metabolic process, which become one of the reasons to disrupt cell machinery by lipid peroxidation, DNA adduct formation, *etc*. and ultimately lead to an oncogenic event. However, several mutations can be overcome by repair mechanism, thus the defective repair system also supports the oncogenic process. Multiple molecular mechanisms are associated with the initiation and progression of different human malignancies, which are centrally linked to the physiological regulators of homeostasis. Thus, activation of cell survival factors like AKT, MAPK and inhibition of apoptosis are known to assist in the proliferation of cancer cells. Several investigations on cancer suggested that the factors connecting link of cell survival to cell death in cancer could be critically important for therapeutic intervention in cancer. Presently, many of the marine natural products are well known for their role in intervening the cancer-associated molecular mechanism; these are directly or indirectly linked to deregulated metabolic pathways or physiological process in cancer progression. The majority of isolated compounds from marine source are peptides, lipids, metabolites *etc*. which are vitally reported for their anticancer activities. Due to their unique anticancer potential, these products also become a choice for the pharmaceutical industry to discover anticancer drugs. From the recent opinions of cancer-associated mechanisms and their targets, marine products emerged as targets for various mechanistic pathways to diminish cancer progression. These compounds

target various major pathways involved in the cancer progression, which are detailed in the subheadings (Fig. **1**).

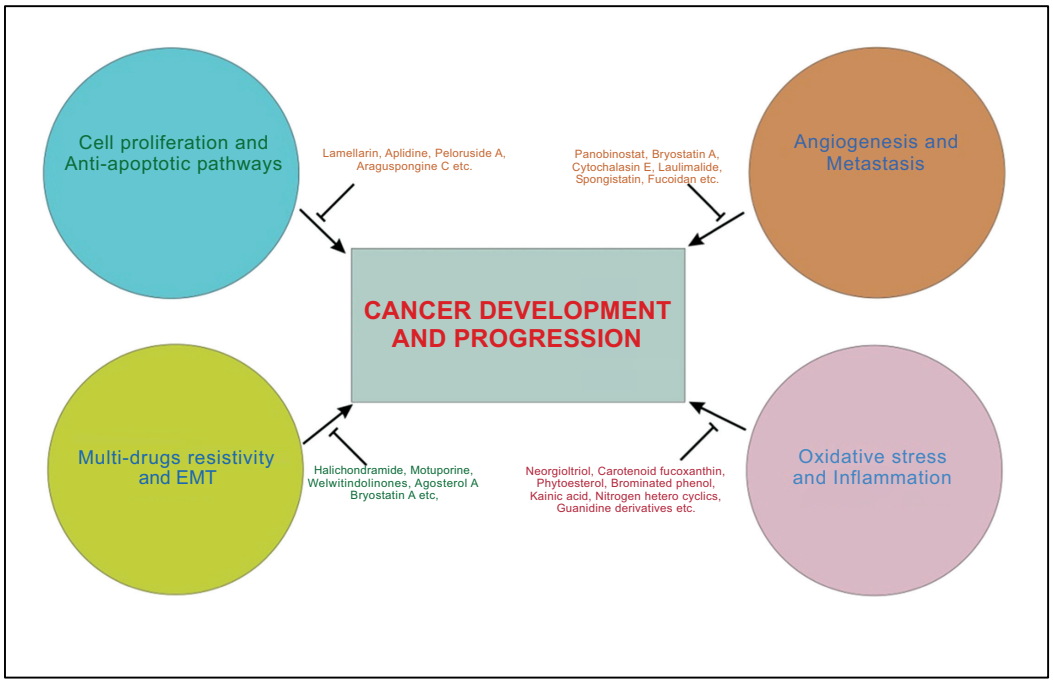

Fig. (1). Current views of the mechanism associated with cancer development and progression. The large-scale marine natural compounds are having unique potency to target these cancer associated pathways. In the figure, few marine compounds are mentioned, which prevent these deregulated processes associated with cancer development and progression.

Targeting Cancer Associated Signaling Pathways

Natural compounds from marine flora and fauna have been explored for their anticancer properties with multiple molecular targets of cancer signaling pathways. It is widely known that cancer cells can grow under constitutive activation of proto-oncogene to oncogenes and or inactivation of tumor suppressor gene with genetic abnormalities. These activation/suppression of various oncogene and suppressor genes followed a multiple signaling pathway, leading to an initiation and progression of cancer. A large number of investigations have demonstrated the efficacy of natural products to control these altered pathways in cancer. As many deregulated pathways implicated in cancer, most commonly defective p53 possess a crosstalk of multiple signaling pathways associated with the proliferation of cancer cell. Several compounds from marine sources exert antiproliferative effects *via* p53 activation. Marine sponge's metabolites (ilimaquinone and ethylsmenoquinone) as activators of p53 pathway

CHAPTER 8

Natural Products as a Unique Source of Anti-Cancer Agents

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Abstract: Cancer is a major public health problem and the second leading cause of premature deaths worldwide, accounting for an incident rate of 2.6 million cases per year, mainly in Europe and the United States. This book chapter describes the historical aspect of cancer, its treatment modalities and history of natural compounds being used as anti-cancer agents. Role of marine natural compounds and their derivatives in cancer prevention, like, alkaloids, amine derivatives, macrolides, peptides and polypeptides are described in this chapter. Both, role of natural compounds extracted from plants and microbial sources are discussed along with their molecular targets and interactions to kill the cancer cells. Most of the medicinal compounds derived naturally are synthesized semi-synthetically for commercial purposes. They are then formulated into proper dosage increasing their costs. But for many natural compounds clinical trials are still to be carried out to validate their use in cancer therapy.

Keywords: Anti-cancer, Cancer therapy, Marine, Microbial, Nutraceuticals, Natural compounds, Plants.

INTRODUCTION

Cancer, a generic term, is defined as a disease that has a group of abnormal cells growing uncontrollably, disregarding the normal rules of cell division. Normal cells always keep getting signals, dictating the cells either to divide, differentiate into another cell or die. This proliferation could be fatal if allowed to continue or spread. Loss of growth controls leads to cancer. Loss of control can occur as a result of mutations in genes that are involved in cell-cycle control. A single event never turns a cell into cancerous one. Instead, accumulation of damage to a number of genes in a long duration of time, leads to cancer. It takes almost 25–35

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Sahdeo Prasad & Amit Kumar Tyagi (Eds.)

years for normal cells to evolve into invasive cancerous cells. As a result of which, many years elapse between the initial events and the development of cancer [1].

Cancer is a group of more than 100 diseases, which develop in a long duration of time. It can occur in virtually any of the body's tissues, due to both, hereditary and environmental factors. So, according to current dogma, cancer is a multi-gene, multi-step disease that originates from a single abnormal cell with a mutated DNA sequence. Successive rounds of mutation and selective expansion of these cells result in tumor growth and progression, consecutively breaking through the basal membrane barrier that surrounds tissues and spreads to distant locations in the body. The phenomenon being named as metastasis.

Cancer, being a major public health problem, is the second leading cause of premature deaths worldwide, which also accounts for an incident rate of 2.6 million cases per year, mainly in Europe and United States [2, 3]. It is projected that the annual deaths due to cancer are about to increase to 13.1 million in 2030 (WHO 2012; http://www.who.int/mediacentre/factsheets/fs297/en/). In developing countries, the cancer incidence prevails by tumor types that are related to viral, genetic mutations and bacterial contamination [4]. Cancer is mostly a disease of lifestyle and is preventable, as most cancers are more prevalent in certain countries than others. For example, incidence of cancer in Unites States is much higher than in the Indian subcontinent (300 *vs*. 98 per 100.000 population) [1, 5, 6]. Hence, there is an indication that plant-based foods are more important in the diet for decreased risk of cancer.

There are evidences of cancer being as old as man, as it's found in the ancient remains of deceased humans and medical literature since the distant past. Cancer has also been noted in plants caused by virus, bacterium or fungi, and being limited by the cell wall [7]. The history of cancer goes back to the times of monarchs known as, Pharaohs, in ancient Egypt [8], Hippocrates (460-375 BC) [1] and even to the Indian system of medicine (5000 years ago), known as, Ayurveda [9, 10]. These ancient medical literatures are the evidences of the fact that physicians used to perform surgeries and also recommended natural products (especially plant products) to the patients. Even today, natural products play a major role in the treatment of cancer either directly or as derivatives (from plants, animals and microorganisms) [8].

TREATMENT MODALITIES OF CANCER

Early diagnosis, better health care facilities and developments in the therapies for

cancer today, has resulted in a remarkable improvement of cancer survival [11]. But in spite of these great progresses made in the progress of cancer treatment and detection, understanding the molecular basis of cancer, there is no definitive cure by the improvements made in the therapies [12 - 14].

The classic treatments for cancer depend on the type, location, and the state of advancement of the cancer. The current paradigm for the primary treatment of cancer is by surgically removing the diagnosed solid tumor [15]. Despite the aggressive surgery measures being used for last so many decades for the treatment of cancer, the mortality rate due to cancer has not decreased to a great extent. Surgeons believe that almost every type of cancer can be treated more successfully by surgery if discovered at an early stage or localized stage [16].

Radiation therapy also remains an important component of cancer treatment. The use of X-rays as a means of cancer treatment was first appreciated after it's discovery by Wilhelm Conrad Rontgen, in 1895 [17]. It is a physical agent used to destroy cancer cells. The ionizing radiations deposit their energy in the cells of the tissue it passes through, hence killing the cancer cells by causing genetic changes in them. High-energy radiations damage the DNA of cells and block their ability to divide and proliferate further [18]. Although the radiation damages both the normal as well as abnormal cells, the goal of this therapy is to minimize the dose to the normal cells that are adjacent to the cancer cells. Moreover, the normal cells are efficient enough, in comparison to cancer cells, in repairing the damage by radiation [19]. Surgery and radiation therapy are mostly used together.

Chemotherapy is also available for the cancer treatment by some toxic compounds that target rapidly growing cancer cells, directly. Specific active proteins in cancer cell signal transduction pathways (for *eg.*, receptors and kinases) are targeted by the new chemotherapeutic drugs. These drugs are very less toxic to the normal cells. Over the years, use of many such drugs have been triumphant in the treatment of cancer. To reduce the side effects associated with these drugs, now new approaches are being studied like (a) the use of new combinations of drugs, (b) therapies targeting cancer cells using liposomal and monoclonal antibodies, (c) use of new chemo protective agents, (d) hematopoietic stem cell transplantation and also (e) the use of agents that have the potential to overcome multidrug resistance.

As stated earlier in the chapter, natural and nutritional compounds have been used for the cancer treatment and prevention throughout the history. High consumption of fruits and vegetables have been linked with the reduced risk of cancer. The cancer-inhibitory potential of nutrients and phytochemicals (from the plants) has

CHAPTER 9

Translation of Natural Products into Clinically Effective Drugs: How Far We Have Gone

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Abstract: Data obtained from Human Genome Project has helped in transition of human diseases from a segmented view to a conceptual continuum. In accordance with this approach, identification of new gene targets has reinvigorated the field of natural product research and predominantly scientists are working to obtain these drugs through the use of high-throughput screening technologies and combinatorial chemistry. It is noteworthy that natural product templates combined with chemistry to selectively produce analogues will have higher chances of success. In this chapter we have attempted to summarize most recent advancements in clinical trials of natural products in different cancers. Keeping in view that structural variants contribute to the genomic landscape, multi-region whole-genome sequencing of hundreds of tumors will be helpful for a better understanding intra and inter-population genetic variability. Moreover, rapidly evolving field of nutrigenomics will play its part by tailoring the food or nutrition to the individual genotype. As we have developed deeper knowledge related to how wide ranging natural products modify cellular mechanisms, we may find that the continuum from pharmaceuticals to nutraceuticals through food-based biologically active phytochemicals will bring the disciplines of nutrigenomics and pharmacogenomics closer together.

Keywords: Apoptosis, Cancer, Metastasis, Phytochemicals, Signaling.

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Sahdeo Prasad & Amit Kumar Tyagi (Eds.)

INTRODUCTION

Cancer is a complicated and genomically complex disease. Data obtained through high-throughput technologies has provided an ever-expanding list of regulators reported to be involved in cancer development, migration and invasion. Overexpression of oncogenes, inactivation of tumor suppressor genes, activation of pro-survival signaling cascades and loss of apoptotic cell death is some of the most extensively studied molecular mechanisms. Large-scale, cancer cell line-based screening of drug sensitivity has emerged as an important dimension of drug discovery and has proved to be helpful in complementing lower throughput, but complicated screens involving 3D and mixed tumors and stromal cultures, animal models and multi-targeted approaches. Off target effects and rapidly development of resistance against chemotherapeutic drugs is a major concern and explosion in genetic, genomic and proteomic information has opened new horizons to unfold the mystery of inter-individual differences in the body′s ability to metabolize and response to nutrients.

PROSTATE CANCER

It is becoming progressively more understandable that genomic heterogeneity within individual prostate glands and between patients stems particularly from copy-number aberrations and structural variants. Subtypes of prostate cancers are being deeply explored using next-generation sequencing, but these subtypes are yet to be thoroughly investigated in the clinical setting for targeted screening and treatment. Research over the decades has added considerable information into the prostate cancer (PCa) biology. Dysregulation of intracellular signaling cascades and Prostate cancer stem cells have also been observed to play a key role in cancer progression and resistance against wide ranging therapeutics.

Dual PI3K/mTOR inhibitor NVP-BEZ235 effectively reduce the population of $CD133^{+}/CD44^{+}$ PCa progenitor cells [1]. NVP-BEZ235 and chemotherapeutic drug Taxotere effectively inhibited tumor growth in mice xenografted with prostate cancer cells [1]. $CD133^{+/}CD44^{high}/AR^{-/low}$ side population (SP) cells isolated from tumorigenic and invasive WPE1-NB26 cells were noted to be resistant to docetaxel. Contrarily, docetaxel was effective against $CD133(^{-})$/ $CD44(^{low})/AR(^{+})$ non-side population cells isolated from the WPE1-NB26 cell line [2].

PC3 and DU145 cells combinatorially treated with NVP-BEZ235 and chemotherapeutic drug (Taxotere) had a 2-fold or greater decrease in $CD133^{+}/CD44^{+}$ progenitor cell populations [1]. NVP-BEZ235 in combination with either 5-FU or

Oxaliplatin 2-fold or greater decrease in the $CD133^{-}/CD44^{-}$ cell population [1]. NVP-BEZ235 and Taxotere synergistically induced 1.5-2.0-fold decrease in $CD133^{-}/CD44^{-}$ population [1]. Combining NVP-BEZ235, which preferentially targets progenitor populations, with chemotherapeutic drugs that target bulky tumors is more useful as compared to monotherapy [1]. Atorvastatin, a 3-hydroxy-3-methyl-glutarylcoenzyme-CoA (HMG-CoA) reductase inhibitor significantly inhibited α1, β1 integrins and phosphorylated levels of FAK and MYPT1. ROCK1 and FAK induced downstream signaling mediated differentiation of $CD133^{+}CD44^{+}$ population derived from prostate cancer tissues however cellular differentiation was markedly inhibited upon atorvastatin treatment [3].

There is a recent evidence of efficacy evaluation of combinatorial therapy consisting of *Phellodendron amurense* bark extract (Nexrutine®) and radiotherapy in prostate cancer patients. The results revealed that treated patients did not show grade 3 toxicity, moreover, toxicities were detected transiently. Post-treatment data analysis indicated that 81% of the patients neoadjuvantly treated had a decline in PSA [4]. Statistically significant double-blind RCT has shown a noteworthy short-term effect on PSA in prostate cancer patients orally administered with a capsule consisting of a mixture of pomegranate, broccoli, turmeric and green tea [5].

Prostate tissue of cancer patients orally administered with pomegranate extract (POMx) was analyzed to study if systemically absorbed pomegranate extracts were converted into Urolithin A. Data indicated that significantly higher levels of Urolithin A levels were detected in POMx treated group. Moreover, 8-hydroxy-2'-deoxyguanosine (8-OHdG), an oxidative stress biomarker was also considerably reduced in POMx treated group [6]. Gene analysis of the specimen obtained from prostate cancer patient administered with short-term soy isoflavone revealed markedly down regulated genes including apoptotic protease activating factor-1 (APAF1), cell division cycle 27 (CDC27), cyclin B2 (CCNB2), cyclin C (CCNC), Ubiquitin-Activating Enzyme (UBE1), cyclin G1 (CCNG1), cyclin G2 (CCNG2), cullin 2 and cullin 3 [7].

Significantly higher levels of sulforaphane are present as compared to its inactive precursor, glucoraphanin. Both glucoraphanin and sulforaphane are known quantitatively in the administered broccoli sprouts. Moreover, glucoraphanin acts as a depot for the bio-active constituent so sulforaphane is slowly cleared from body. Since 2012 a pilot study is evaluating how broccoli sprout extract dose-dependently exerts biological effects on Dysplastic Nevi, as precursory lesions

SUBJECT INDEX

A

Abnormal cells 129, 147, 149
Acanthopanax Senticosus 106, 112
A-carotene 70
Acid(S) 6, 8, 13, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 50, 51, 52, 53, 75, 76, 93, 94, 95, 96, 111, 133, 160,
  11-keto-β-boswellic 35, 37, 41, 43, 44, 45, 46, 47, 50, 51
  α/β-boswellic 35, 37, 39
  α-boswellic 35, 36, 39
  β-boswellic 36, 37, 43, 44, 48, 50, 51, 53
  O-acetyl-11-keto-β-boswellic 37, 40, 41
  O-β-D-xylopyronosylellagic 96
  acetyl-11-keto-β-boswellic 37, 39, 51
  Acyl derivatives of boswellic 40, 42
  arachidonic 160
  ascorbic 111
  betulinic 6, 75, 76
  ellagic 75, 95
  fatty 9, 75, 133
  hydroxamic 52
  ursolic 6, 8, 13
Acquired immune deficiency syndrome (AIDS) 88
Actinomycins 165
Activities 21, 26, 32, 40, 43, 46, 50, 51, 87, 92, 94, 133, 153, 158
  anti-arthritic 32, 50, 51
  anti-proliferation 40, 46
  antiproliferative 92, 94
  biological 21, 26, 43, 87, 133, 153
  higher 158
Adenocarcinoma 72
Adverse drug reactions (ADRs) 188
Agelasine 154
Agents 65, 75, 76, 80, 81, 149, 150, 165, 166, 167
  anti cancer 167
  natural 75, 81
  new anticancer 150
AKBA in PC-3 cancer cell lines 48
Alkaloids 90, 91, 126, 133, 134, 147, 151, 153, 154
Allanxanthone 95
Alliinase 21, 22
Allyl disulfide 23
Allyl methyl sulfide (AMS) 23
Aloe vera mouthwash 115, 116
Amaranthaceae 107
Amaranthus paniculatus 107, 108
Angiogenesis 40, 76, 77, 130, 153, 161, 162, 163
Anthracycline 165
Anti-cancer 32, 35, 38, 43, 147, 160, 162, 166
Anti-cancer activities 5, 6, 13, 20, 21, 25, 41, 44, 48, 49, 52, 66, 71, 75, 89, 90, 91, 92, 95, 98, 112, 115, 116, 126, 130, 134, 138, 153, 162, 164, 167, 189
  exhibited potential 90
  illustrated 167
Anti-cancer agent 12, 71, 98, 115, 125, 152, 153, 165
  derived 152, 153, 165
  potential 98
Anti-cancer cell lines 90
Anti-cancer compounds 4, 131, 134, 136, 137, 165
  clinical 134
Anti-cancer drugs 32, 87, 134, 137, 138, 162
  new 32, 87
  plant-derived 162
  potential 87
Anti-cancer drugs development 133
Anti-cancer effects 10, 12, 105, 108, 134, 136, 163
  displayed 12
  exhibited 10
Anti-cancer marine compounds 131
Anti-cancer targets, validated 99
Anti-cancer therapy 153
Anti-inflammatory activities 5, 6, 20, 71, 135
Anti-inflammatory drugs 50
Antioxidant effect 24, 113
Anti-proliferative activity 39, 40, 41, 108, 134, 135, 136, 137, 138
Anti-tumor activity 38, 134, 137, 157, 159, 162
Apoptosis 6, 9, 12, 25, 26, 39, 40, 41, 42, 43, 45, 47, 49, 52, 66, 69, 70, 71, 72, 73, 76,

77, 78, 79, 80, 96, 110, 126, 128, 129, 130, 133, 134, 136, 137, 138, 153, 154, 156, 160, 161, 162, 182
induced 25, 42, 43, 45, 49, 52, 69, 72, 76, 96, 133, 153
inducing 9, 26, 133
mediated 26, 79
radiation-induced 110
Apoptosis induction 26, 129
Apoptosis pathways 71
Ardisiaquinone 92, 93
active compounds being 92
Ardisiaquinones 92
mixture of 92
ATP-binding cassette (ABC) 128
Azadirachta indica 109, 110

B

Benzydamine mouthwash 115, 116
Biophytum sensitivum 107, 111, 112
Biselyngbyaside 155
Bleomycin 153, 165
Body gamma irradiation 111, 112
Bone marrow cells (BMC) 73, 187
Boswellia sp 32, 34
Boswellic acid nanoparticles 42, 52, 54
structure activity relationship of 52, 54
Breast cancer 5, 6, 7, 8, 10, 13, 67, 75, 76, 93, 106, 116, 139, 150, 156, 157, 165
diagnosed 10
late stage 139
negative 7
Breast cancer cell lines 69, 162
Breast cancer cells 70, 76, 128, 130, 135, 137, 162
growth of 70
human 162
Breast cancer 8, 128
incidence 8
resistance protein (BCRP) 128
Broccoli sprout extract (BSE) 184, 185

C

Cancer 4, 5, 6, 7, 8, 9, 11, 12, 13, 66, 68, 72, 74, 78, 80, 81, 107, 130, 135, 136, 152, 153, 160, 163, 165, 167, 185
bladder 8, 160
bone 13
colorectal 6, 8, 11, 66, 135, 185
endometrial 11, 72
gastrointestinal 12
head-neck 7
hematopoietic 9
human 4, 81, 136, 163, 167
kidney 9
liver 107
metastasized 74
metastatic 130
metastatic squamous cell 153
neck 6, 8, 13, 78, 107, 165
oral 5
pediatric 152
peritoneal cavity 152
renal 152
skin 68, 80
stomach 11
testicular 81, 160
Cancer-associated mechanisms 126
Cancer-associated molecular mechanisms 126
Cancer being 148
Cancer care 75
Cancer cell death 129
Cancer cell lines 39, 47, 48, 74, 91, 93, 98, 133, 134, 135, 136, 137, 138, 154, 155, 156, 161, 167
Cancer cell proliferation 129
Cancer cells 5, 6, 9, 10, 13, 25, 47, 52, 66, 74, 77, 79, 81, 88, 106, 126, 127, 128, 129, 130, 133, 134, 135, 136, 137, 138, 139, 147, 149, 150, 154, 161, 162, 183
growing 149
resistant 128
targeting 128, 149
Cancer cells growth 135
Cancer cell signal transduction pathways 149
Cancer cells lines 156, 157
human 157
Cancer chemo, display 9
Cancer chemoprevention 5, 64, 67, 79, 125, 139, 150
potential 139
properties 79

strategies 150
Cancer chemotherapy 88
Cancer deaths 87
Cancer development 3, 5, 7, 9, 10, 72, 78, 125, 126, 127, 183
Cancer disease 65
Cancer drugs 67, 139
Cancer immunotherapy 164
Cancer incidence 8, 125, 148
Cancer inhibition 74
Cancer inventory 167
Cancer management 130, 134
Cancer occurrence 65
Cancerous 147
Cancerous cells 25, 148
  invasive 148
Cancer prevention 9, 10, 14, 64, 65, 73, 79, 106, 126, 130, 133, 139, 147, 154, 158, 161, 163, 164, 166
  activity 126
  properties 106
  research 65
  actions 9
  natural marine products 130
Cancer progression 80, 126, 127, 134, 183
  delay 80, 134
Cancer signaling pathways 127
Cancer suppression 129
Cancer survival 149
Cancer therapeutics 150
Cancer therapy 52, 128, 147, 150, 151, 161, 164
Cancer treatment 3, 33, 87, 88, 129, 149, 150, 153, 166, 167
  modern 88
Cancer treatment measure 3
Cancer types 67, 71, 76, 81, 128, 129, 151, 160, 161, 165, 167
  multiple 76
Carcinogenesis 66, 81, 126, 131, 139, 140
Cardioprotective 21, 68
Carotenoids 7, 69, 108, 134, 151
Caspase activation 25, 41, 96
Cell cycle arrest 25, 52, 71, 76, 77, 128, 134, 153
Cell death 3, 10, 41, 42, 126, 128, 129, 133, 135, 137, 139
  inducing 41
Cell differentiation 39, 40
Cell growth 9
Cell lines 10, 52, 92, 96, 136, 137, 138, 155
  drug-resistant cancer 92, 96
  female reproductive cancer 138
  human colorectal cancer 10
  human lung cancer 155
  metastatic melanoma cancer 137
  multiple human cancer 136
  non-cancer keratinocyte 137
  panel of human cancer 52
  resistant cancer 138
Cell proliferation, inhibiting cancer 130
Cells 5, 6, 12, 13, 25, 52, 64, 77, 79, 80, 81, 92, 93, 105, 112, 130, 136, 147, 149, 154, 156, 159, 160, 161, 162, 165, 183
  endothelial 154, 156
Cell signaling molecules 3, 5, 9
Cell signaling pathways 12, 76, 125, 164
Centella asiatica 107, 113, 114
Chemopreventive 68, 74, 75, 76, 77, 78, 79
  activities 68, 74, 75, 78
  agents, natural 76, 77, 78, 79
Chemo-radiotherapy 110
Chemotherapeutic 3, 6, 80, 87, 128, 130, 139, 183, 184, 187, 188
  agents 80, 87
  drugs 3, 6, 80, 128, 130, 139, 183, 184, 187, 188
Chemotherapy 3, 88, 110, 112, 114, 115, 128, 149, 150, 153, 185
Chitosan 134, 137
Cholesterol 21, 25, 164
Cisplatin 72, 153, 185
Colon cancer 9, 10, 11, 12, 13, 66, 67, 69, 72, 73, 76, 79, 158, 166
  cells 10
    human 72, 79
  incidence 9
  models 66
Colorectal adenocarcinoma 136, 157
Colorectal cancer growth 11
Colorectal cancer HT29 cells 11
Colorectal cancer lines 135
Commiphora myrrha 162
Complete remission (CR) 187
Compound glycyrrhizin 114
Compounds 4, 6, 8, 9, 11, 22, 23, 25, 32, 34, 35, 36, 37, 39, 41, 43, 46, 47, 52, 54, 64, 65,

74, 75, 78, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 125, 126, 127, 130, 131, 132, 133, 136, 137, 138, 139, 149, 151, 153, 154, 155, 156, 157, 158, 159, 160, 163, 167, 189
active 159
botanical 151
chemical 139, 151, 158
containing 22
cytotoxic 97, 98
diterpene 136
extract 139
indole 138
inorganic 35
nontoxic 137
non-volatile 35
novel 153
nutritional 149
phenolic 25, 153
plant-derived 158
polyphenolic 189
soluble 23
synthesized 47, 52
toxic 149, 154
volatile 35
Compound Sophora flavescens 187
Compounds target 64, 166
natural 64
Conditioned taste aversion (CTA) 114
Consumption, wholegrain food 10
Corals, soft 134, 135, 157
Coriolus versicolor 73
Coronopus Didymus 107, 113
Crassocolides 135, 136
Curcuma longa 65, 160
Curcumin extracts 160, 185
Curcuminoids 65, 160, 187
Current clinical management of cancer 88
Cyanobacteria 133
Cyclic depsipeptides 131, 138, 155
Cyclic organic compounds 92
Cyclooxygenases 66, 160, 161
Cytokines 73, 78, 79, 109, 112, 130, 150
Cytotoxic activity 81, 98, 136, 155, 156, 157, 159
compound showed 155
exhibited 155, 156, 157
Cytotoxic drugs 88, 130
Cytotoxicity 11, 39, 43, 44, 46, 47, 48, 52, 96, 108, 129, 154
induced 11
loss of 44, 47

D

Daidzein 8, 9, 72
Daunomycin 165
Decreased skin cancer 68
Delayed type hypersensitivity (DTH) 112
Dendritic cells (DCs) 130
Depict anti-cancer property 166
Depicted anticancer activity 161
Derivatives 45, 46, 47, 48, 49
2-cyano-1-en-3-one 45, 46
modified 11-keto-β-boswellic acid 47, 48, 49
pyrazole 46, 47
Destroy cancer cells 149
Diallyl disulfide 22, 23
Diallylthiosulfinate 21
Dietary compounds 3, 4, 14, 150
natural 14
Diketosteroid 157
Diterpenoid Compounds 157
DMBA model of mammary cancer in rats 72
DNA binding 78
DNA synthesis 39
Dolabella auricularia 131
Doxorubicin hydrochloride 154

E

Effective synergy 187, 188
Effects 25, 42, 80, 153
anti-cancer 153
synergistic 25, 42, 80
Efficacy of cisplatin in gastric cancer cells 72
EGCG in breast cancer cells 76
EGCG in prostate cancer cells 76
Elephantopus mollis 90, 98
Emblica officinalis 107, 115
Emblica officinalis extract (EOE) 115
Endoperoxide 44, 45
Enzymes 24, 32, 39, 66, 73, 74, 161, 164
Epidermal growth factor receptor (EGFR) 66, 78, 79, 150

Epigallocatechin-3-gallate 67, 163
Epimerization 43
Erysodine 90
Erysotrine 90
Erythraline 90
Erythrina 89, 90, 91
  abyssinica 89, 90
  excelsa 89, 91
  senegalensis 89, 91
Estrogen 67, 75, 162
Exhibited anti cancer activity 155

F

Flavonoids 13, 20, 25, 71, 90, 91, 108, 109, 111, 161, 189
Fractions, crude alkaloidal 90
Frankincense 33, 35, 162, 163
Fruits 3, 4, 5, 6, 7, 8, 11, 65, 70, 149, 167
  pomegranate 70
  sour jujube 6
  strawberry 6
Fruits and vegetables 5, 6, 7, 8, 65, 69, 75, 149, 150
  consumption of 7, 8, 149
  intake of 7, 8

G

Ganoderma lucidum 73
Garlic 20, 21, 22
  chopped 20, 22
  crushed 21
Garlic extracts 12, 21, 24
  aged 12, 21
Garlic organosulfur compounds 21
Garlic orgaosulfur compounds 24
Garlic supplements 21
Gastric cancer 13, 26, 134
  induced 134
Gastric cancer cells 72, 136
  human 136
Gefitinib 187
Gemcitabine 6, 186, 188
Ginsenosides 74, 75, 110
Glucoraphanin 73, 74, 184
Glutathione 10, 107, 108, 111, 115
Glutathione-S-transferase (GST) 113
Grandibracteata 93, 94
Grandibracteoside 93, 94
Green tea polyphenols (GTP) 67, 78, 79
Growth 5, 6, 9, 25, 66, 69, 70, 75, 78, 80, 113, 133, 136, 150, 154, 155, 156, 157
  cellular 78
Growth factors 13, 64, 77, 78
Growth inhibition 77, 79
Guttiferone 96, 97

H

Healers, traditional 87, 89
HeLa cancer cells 11
HEP-2 cytotoxic activity 91
Hepatocellular carcinoma 6, 8, 136, 186
Hep-G2 cell lines 91
Hormones 65, 150
HT29, colon cancer cell lines 156
HT29 colon cancer 78
Human bladder cancer 76
Human hepatoma cells 25, 72
Human peripheral blood lymphocytes (HPBLs) 106, 108
Human umbilical vein endothelial cells (HUVEC) 70, 162
HUVECs cancer cells 46, 47
Hybrids 50
  synthesized 50
Hydrophobic linkers 52
Hypercalin 95
Hypericum flowers 109
Hyperplasia, benign prostate 8, 69

I

Ibuprofen 50
Immune responses 80, 164, 165
Immunomodulation 112, 129, 130
Immunomodulatory 110, 111, 116
Immunoprevention 79
Inflammation-to-cancer sequence 75
Inflammatory biomarkers 186, 187
Inhibitory effects 6, 73, 78, 161, 162
Irinotecan 152, 159, 185
Isoflavones 8, 9

Isogarcinol 96, 97
Isoneorautenol 91
Isoxanthochymol 96, 97
Isoxazoles 46, 47

K

Kanglaite Injection 186
Kendarimide 128, 129

L

Lagunamide 155
Lamellarin 128, 129, 153, 154
Legumes 3, 4, 8, 9, 11
Leukemia 5, 6, 66, 79, 136, 152, 159, 165
Linear peptide 131
Liver cancer cells 129
Liver cancer Hep G2 cells 41
Lung cancer 7, 8, 70, 73, 107, 116, 152, 156, 160, 165, 185
  increased 7
Lung cancer cell growth 70
Lung cancer risk 7
Luteolin sensitizes cancer cells 71
Lymphocytes 94, 115, 136
Lymphoma 81, 152, 160, 165

M

Macrocyclic lactone 129, 131, 134, 135
Macrolides 147, 153, 154, 155
Maharshi amrit kalash (MAK) 167
Malignancies, human 126, 134, 135, 138
Malignant cancer cells 113
Mammary cancer 72
Marine bioactive compounds 128
Marine compounds 125, 127, 129, 130, 134, 139, 140
  natural 134
Marine extracts 130, 139
Marine fauna 134
Marine fishes 139
Marine flora 127, 130, 133, 134
Marine flora and fauna 125, 127, 130
Marine micro-flora 133
Marine mollusks 137, 138
Marine natural compounds 154
Marine organisms 126, 134, 153, 167
Marine products 126, 128, 139, 155
Marine resources 125, 128, 139
Marine sources 126, 127, 139, 153
Marine sponges 135, 154, 155, 156, 157
MDR in breast cancer cells 137
Median survival time (MST) 187
Medicinal compounds 147, 167
  derived 167
Medicinal plants 13, 87, 88, 89, 111
Medicine 21, 38, 65, 66, 88, 96, 108, 110, 111, 113, 114, 139, 148, 151, 153, 158, 163, 166
  modern 151, 158
  traditional 96, 108, 110, 111, 113, 139, 151, 166
Medulloblastoma cancer cell line 135
Melanoma 155
Metabolites 89, 90, 126, 133, 134, 136, 139, 151, 156, 185
  isolated 89, 90
  secondary 89, 126, 133, 134, 136, 156
Metastasis 6, 9, 10, 25, 26, 74, 77, 78, 107, 148, 182, 186
Methanol extract 92, 95, 96, 111
Methyl thiazolyl tetrazolium (MTT) 108
Migration inhibitory factor (MIF) 162
Mitogen-activated protein kinases (MAPK) 66, 126, 161, 164
Molecules 4, 22, 26, 32, 36, 38, 39, 40, 43, 46, 48, 50, 52, 54, 75, 78, 81, 153
  hybrid 50
  marine anticancer 153
  parent 46, 48
Mucositis, induced 115, 116
Multi drug resistance (MDR) 128, 129
Myeloma, multiple 5, 6

N

Natural compounds being 147
Natural molecules 64, 77, 79, 80, 81
Natural product research 167, 182
Neck cancer risk 7
Neobavaisoflavone 91
Neutraceuticals 166

NF-κB signaling pathways 77, 78
NF-κB Signalling 40
Nitrogen atom 46, 91
Nitrogen-containing organic compounds 90
NMR spectroscopic data 37
Non-small cell lung cancer (NSCLC) 186, 187
Novel anticancer activity 139
Novel anticancer drugs 97, 139
Novel pharmacological compounds 167
Nutraceuticals 13, 14, 81, 125, 139, 147, 151, 166, 182
  dietary 13
Nutrigenomics 182

O

Oil, neem 109, 110
Omega-3 75
Oral squamous cancer cells 71
Order anthoathecata 136, 137
Organosulfur compounds 20, 21, 73
Ovarian cancer 66, 115, 152
  progressive low-grade 152

P

Paclitaxel 92, 152, 158
Pancreatic cancer 6, 10, 154, 155, 186
  advanced 186
  human 6
Pancreatic cancer cell line 42
Partial remission (PR) 187
Phenolic hydrogen bond donor 91
Phytochemicals 5, 11, 88, 105, 106, 107, 115, 116, 133, 149, 158, 182, 189
Plant extracts 90, 108, 114, 166, 189
Plants 113, 114, 133
  flowering 114, 133
  genus of 113
Pneumonitis, radiation-induced 108, 109
Polyphenols 6, 7, 8, 11, 66, 67, 70, 77, 126, 133, 151, 153, 156
Polysaccharides 34, 35, 73, 130, 133, 134, 151, 156, 185
Pomegranate 70, 75, 184
Pomegranate extract 70, 184, 185
Pomegranate fruit extract 70
Post relapse disease-free survival (PRDFS) 188
Progression-free survival (PFS) 187
Prostate cancer 6, 8, 11, 69, 70, 72, 74, 75, 79, 81, 93, 138, 150, 183
  metastatic 150
  sensitize 81
Prostate cancer cell(s) 40, 67, 69, 71, 72, 73, 74, 76, 136, 156, 157, 183
  growth 72
  line apoptosis, resistant 67
  lines 69, 72, 136, 156, 157
  proliferation 71
  chemo-resistant androgen-independent PC-3 40
  metastasized 74
Prostate cancer chemoprevention 75
Prostate cancer lines 70
Prostate cancer patients 72, 184
Prostate cancer risk 10
Prostate cancer stem cells 183
Prostate cancer tissues 184
Prostate-specific antigen (PSA) 70, 71, 73, 184
Protein kinases 13, 161, 162
Proteins 128
  breast cancer resistance 128
  transporter 128
Punica Granatum 161
Pyrazole 46

Q

Quinones 92, 156

R

Radiation 71, 72, 81, 105, 106, 107, 108, 111, 112, 113, 114, 115, 116, 149
  damage 105, 106, 113, 149
  therapy 116, 149
Radioprotection 21, 108, 109, 113, 116
Radioprotective effect 106, 116
Radioprotectors 106, 111
Radiotherapy 13, 88, 106, 110, 115, 153, 184, 186, 187
Rapamycin 114, 165
Reactive oxygen species (ROS) 42, 115, 160, 163

Reduced cancer risks 7, 12, 163
Reduced risk of cancer 10, 11, 149, 150
Reduction, breast cancer risk 80
Reverses P-glycoprotein 129
RKO cancer cell lines 135
Role of marine natural compounds 147, 154

S

Saponins, monodesmosidic 51
Scavenging activity 161
Scopoletin 96, 97
Sensitivum 111
Sepia ink oligopeptide (SIO) 156
Sesquiterpenes 35, 135, 136
Signaling pathways 26, 76, 78, 127, 131, 134, 135, 162, 189
  multiple 127, 131
Signal transducers 79
Signal transduction pathways 163, 166
Significant anticancer activity, displayed 52
Sipholenol A 128, 129
Soy isoflavones 8, 81
STAT3 6, 66, 79
Stem bark 89, 92, 93, 96
Steroids 134, 136, 157
Structure-activity relationship (SAR) 33, 43, 52, 54, 91
Sulforaphane 73, 74, 184
Sulfur compounds 21
Superoxide dismutase 24, 108, 112, 113
Suppress colorectal cancer growth 11
Synthesis 23, 42, 43, 52, 80, 87
  chemical 23, 80
Synthetic drugs 80, 81
Systems 36, 65, 73, 74, 79, 105, 112, 151, 160, 188
  immune 65, 73, 74, 79, 112, 188
  nervous 105, 160

T

Target genes 76, 77
Targeting cancer associated signaling pathways 127
Tea polyphenols 64, 66, 67, 79, 163
  green 67, 79
Teniposide 159, 160
Tephrosia Purpurea 107, 114
Terpenes 151, 152, 157
Terpenoids, higher 35
Tetrahydroxybenzophenone 96, 97
Theaflavins 164
TNF-related apoptosis-inducing ligand (TRAIL) 128
Topoisomerase 39, 40, 154, 159, 164
Topotecan 152, 159
Trabectedin 128, 132, 138
Traditional chinese medicine (TCMs) 73, 110, 151, 163, 187
Triple-negative breast cancer 154
Triterpenes 32, 35, 36, 37, 38, 40, 41, 75, 76, 153
  pentacyclic 32, 37, 38, 41
Triterpenic compounds 36, 37
  pentacyclic 37
Triterpenoids 32, 33, 93, 94
Tumor cells 6, 12, 40, 79, 80, 94, 129
  pancreatic 6, 79
Tumor development 4, 11, 129, 130, 158

U

Urolithin A 184

V

Vascular endothelial growth factor (VEGF) 6, 25, 71, 79, 162
Vinblastine 152, 159, 162
Vinca alkaloids 66, 159
Vincristine 152, 159, 162
Vinorelbine 66, 152, 159, 185
Viscum album 188
Vitamins 7, 69, 96, 108, 109, 111, 139, 151

W

Walnut-induced inhibition of colorectal cancer growth 11

X

Xanthones 94, 95
X-ray irradiation 109