THERAPEUTIC IMPLICATIONS OF NATURAL BIOACTIVE COMPOUNDS

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Frontiers in Bioactive Compounds

(Volume 3)

(Therapeutic Implications of Natural Bioactive Compounds)

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Frontiers in Bioactive Compounds

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FOREWORD

We take the opportunity to communicate with you, through this foreword message of the book series with thematic focus on **'Frontiers in Bioactive Compounds (Volume 3) Title: Therapeutic implications of Natural Bioactive Compounds'**.

The nature has provided us enormous genetic potential which has evolved through ages and appears not only in form of biological diversity but also in form of biologically active molecules called bio-active compounds. Many bioactive compounds obtained from natural sources include, phenolics, alkaloids, tannins, saponins, lignin, glycosides, terpenes etc. have been studied thoroughly for therapeutic applications with potential use in pharmaceutical industry.

The assessment of wide-ranging therapeutic potentials of these bioactive compounds has led to the discovery of many modern drugs in recent times. In the present era, it is believed that the natural product-based medicine is considered as the most suitable and safe to be used as an alternative medicine due to their low or no side effects at the effective doses. Moreover, World Health Organization aims to increase the integration of traditional medicine in order to improve health care system. Therefore, natural products research has become a thrust area among scientific community aimed toward understanding the chemistry, analytical methodologies, biosynthetic mechanisms, and pharmacological activities of several natural bioactive compounds. Thus, it is prime interest of researchers to develop understanding about various natural bio-active compounds in order to promote the drug discovery research and to complement the medical world by developing novel drug molecules with superior bioactivities.

The present book series entitled **'Frontiers in Bioactive Compounds (Volume Title: Therapeutic implications of Natural Bioactive Compounds)'** includes 13 chapters contributed by many academicians, scientists, and researchers from various leading institutes from India and abroad. The editors have made enormous and successful effort to assemble a huge variety of knowledge on structures and therapeutic potential of various natural bioactive compounds present in plants, fungi, algae, marine organisms etc. Chapter contributors have extensively reviewed the therapeutic role of various bioactive compounds against many health disorders in human such as COVID-19, cancer, diabetes, immuno-modulators, neurodegenerative changes and many diseases of farm animals.

We believe this book surely provides updated information on the structure, properties and much therapeutic application of various natural bioactive compounds to graduate, undergraduate students, teachers, food scientists, nutritionists, pharmaceuticals, physicians, food industrials, as well as for health-conscious consumers. We congratulate the editors **Dr. Mukesh Kumar Sharma** and **Dr. (Mrs.) Pallavi Kaushik**, and all contributing authors for bringing the collection of their noble piece of work and also for the grand success of this book.

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PREFACE

Bioactive compounds have been used as traditional medicines since ancient times. Therefore, the study of therapeutic potential of various bioactive compounds against many diseases and health disorders has been an important area for scholars, academicians, doctors and pharmaceutical industry people.

There are very few books available currently to cover such a wide spectrum of topics. Therefore, this book is a definitive compilation of chapters which are mainly focused on the therapeutic implications of bioactive compounds derived from natural sources like bacteria, algae, fungi, plants and animals. Various chapters in the book incorporate the knowledge based on traditional medicine with recent advances in bioactive molecular research and their pharmaceutical and industrial importance.

A brief note on the 13 chapters of this book is given as follows:

Chapter 1 highlights the recent development strategies of flavonoids prevailing in the field of neurodegenerative diseases like Alzheimer's, Parkinson's, and multiple sclerosis, along with their limitations and strategies to encounter the challenges.

Chapter 2 deals with recently discovered plant and marine originated natural compounds for cancer therapeutics. This is an attempt to consolidate data on various bioactive compounds concerning with more targeted and innoxious approach along future outlook.

Chapter 3 gives a comprehensive idea about natural bioactives from plants and other sources with antibiofilm activity. Clinical validation of these bioactives will aid the medical field with alternate preventive and treatment methods against pathogenic biofilms.

Chapter 4 is a compilation of research on SARS CoV-2 with its life cycle, pathogenesis, and currently used drugs for treatment, including the synthetic ones, medicinal herbs and the specific bioactive compounds found efficacious against COVID- 19.

Chapter 5 discusses the common groups of plant derived bioactive compounds with anti-diabetic potential by virtue of their potential to modulate various pathways involved in the regulation of blood glucose levels.

Chapter 6 focuses on therapeutics and industrial application of the algae derivatives' primary and secondary metabolites.

Chapter 7 presents an overview of the traditional uses, phytochemical constituents and various pharmacological properties of F.vulgare and T.ammi seeds.

Chapter 8 is an attempt to consolidate information on recently observed bioactive compounds which have aided in unrelenting research to explore their potential use for the treatment of various livestock diseases.

Chapter 9 provides an overview on the isolation and characterization of the bioactive compounds derived from Indian medicinal plant H. indicus, their biological properties with particular emphasis on anti-diabetic potential.

Chapter 10 deals with different works and approaches employed for utilizing tea polyphenols against pesticide induced toxicity carried out internationally and nationally, along with their future prospects.

Chapter 11 emphasizes upon the role of various bioactive compounds derived from fungal sources with their pharmacological importance.

Chapter 12 focuses on a few extensively scrutinized immunomodulatory phytocompounds from medicinal plants such as Tinospora cordifolia, Andrographis paniculata, Curcuma longa, Zingiber officinale, Allium sativum, Terminalia chebula and Piper longum which have been studied in experimental (in vitro and in vivo) models and few compounds have exhibited good therapeutic potential in clinical trials also.

Chapter 13 describes the bacteria-derived bioactive compounds like antibiotics, enzymes and other secondary metabolites like Gallic acid, Amicoumacin, Prodigiosin, Nystatin, Spinosad, Milbemycin, Lipstatin, Subtilin, Albaflavenone, Mollemycin A which have been studied for their inhibitory action against bacteria, fungi, insects, pests, *etc*.

We appreciate the tremendous efforts of the authors from renowned institutions of India, Japan and China for sharing their pieces of expertise in the contributed chapters. We shall also extend a hearty thanks to Bentham Science Publishers for providing the opportunity to contribute as editors of this book.

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CHAPTER 1

Flavonoid Based Bioactive for Therapeutic Application in Neurological Disorders

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Abstract: Flavonoids belong to a class of natural, polyphenolic dietary compounds which modify the neuropathological state of the brain. Some flavonoids like quercetin and other, reduce the inflammation, carcinogenicity, and oxidation promotes neuroprotection and comprises the major component of cosmetics, medicinal and dietary supplements. Daily intake of flavonoids helps to mitigate the risk of several neurological disorders like Alzheimer's disease, Parkinson's disease, multiple sclerosis, *etc*. Flavonoids exhibit their pharmacological effect through various mechanisms like cholinesterase inhibition, scavenging free radicals, memory enhancement *via* attenuation of amyloid plaques, tau targeting detoxification and neural antiinflammation. Administration of flavonoids to biological system has to pass through several biological checkpoints like first pass metabolism, intestinal absorption, and entry into blood brain barrier. Flavonoids exhibit difference in pharmacokinetic and pharmacodyanmic profile due to difference in their structures. Recent literature reports have proved promising therapeutic potential in neurological disorders. This chapter highlights the recent development of flavonoids prevailing in the field of neurodegenerative, its limitations and drug delivery approaches to encounter the challenges.

Keywords: Flavonoids, Alzheimer's, Parkinson's, Natural Biological, Neurodegenerative disorder.

INTRODUCTION

Flavonoids are plant derived secondary metabolites [1]. Flavonoids are long-serving in treatment of diseases [2]. Flavonoids have been considered as good therapeutic agents due to their easy extraction, diversification, and abundance. To date, around 7,000 or more different types of flavonoids have been discovered from plants (vegetables and fruits). These naturally occurring metabolites possess numerous beneficial effects and mitigate plenty of health problems thus plays a

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significant role in drug designing and discovery [3, 4]. Flavonoids own good affinity for several body proteins, excellent antioxidant activity, metal chelation ability, and additionally can alter enzymes, receptors, and transporters [3, 5, 6]. There are ample amount of research studies advocating its anti-cancer, anti-inflammatory, anti-diabetic, neuroprotective, antimicrobial activities, and as cardiovascular drugs [6 - 10]. Some studies reported it as a cognitive enhancer, while others claim flavonoids as therapeutic against Alzheimer's disease (AD). These results were observed in preclinical evaluation [11 - 13]. It was also reported that flavonoids and its derivative metabolites can interact with several subcellular targets [14] for example, interaction of flavonoids with PI3-kinase/Akt and ERK signalling pathways receptors can accelerate the neuroprotective proteins expression and increase neuronal count [15 - 18]. Flavonoids enhance cerebrovascular functionality thus improving blood flow the brain and triggers the generation of neurons that ultimately results in better cognition. There are numerous other mechanisms that reported the beneficial effects of flavonoids.

Flavonoids have ability to suppress the inflammation mediated neuronal apoptosis, inhibition of abnormal β and γ secretase and curb the oxidative stress, thus can debilitate the progression and onset of AD [19, 20]. Thus, flavonoids can act as neuroprotectants by improving the quality and quantity of neurons.

Flavonoids Chemistry and its Classification

Flavonoids are polyphenols with chemical structure involving two benzene rings interconnected with a pyran ring, one is amalgamated with pyran ring while the other is attached as a substitute in pyran ring. On the basis of benzene ring substitution, saturation of pyran ring, derivatization can be possible that owned physicochemical properties suitable for neuroprotectant.

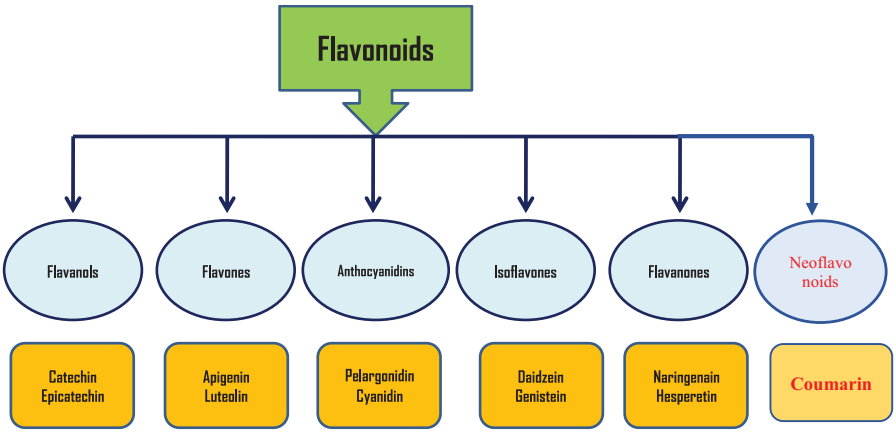

Fig. (1). (a) Flow chart presentation of flavonoids.

Flavonoids Classification

Depending on the benzene ring position and pyran attachment along with extent of oxidation and unsaturation of pyran ring, flavonoids are chemically classified into different groups having different pharmacological properties discussed below (Fig. **1** and Table **1**).

Table 1. Summary of flavonoids obtained from medicinal plants' with potential neuropharmacological properties.

Flavonoids	Source	Study Design	Results	References
Anthocyanin flavonoids	Blackberry extract Grape juice	Male wistar rats/APP/PS1 model of AD Male Wistar rats/ Lipopolysaccharide/ interferon-γ-induced glial cells activation	Behavioral and motor improvements, Decrease (TNF-α and IL-1β), nitric oxide production, Down-regulation of CNTF, CINC-3, IL-10. Antioxidants, scavengers of reactive oxygen species (ROS) and reactive nitrogen species (RNS).	[70-73]
Epigalocatechin Galate (EGCG) Genistein	Green tea	Anti-amyloid study Secretases inhibition assays EGCG mediated estrogen receptors (Estrogen receptor-α Phosphoinositide 3-kinase, Ak) modulation. Anti-tau study on AD Transgenic animals Antioxidant studies in neuronal cells	Suppress the expression of oxidative stress factors, and reduce neuronal apoptosis and later protein expression in PI3K, p-AKT and eNOS signaling pathway. Reduced ERK and NF-kB pathways Suppressed Ab induced lipid peroxidation Inhibit Ab-induced apoptosis, Caspase activity Improve Neuronal survival Increase Non-amyloidogenic APP Decrease Fibrillogenesis decrease Formation of sarkosyl-soluble phosphorylated tau isoforms low Risk of Parkinson's disease low Neurodegeneration decrease ischemic hippocampal injury high PI3-kinase activity Increase Nigral damage *via* scavenging of free radicals	[74-77] [78-80] [81-83]

CHAPTER 2

Potential Uses of Plant and Marine Derived Bioactive Compounds for Cancer Theragnostic

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Abstract: The evolution of novel strategies for application in all facets of cancer theragnostic has shown great progress in the past several decades. Bioactive compounds collected from plants and marine natural provenances have now been accredited as the crucial stepping stone to endow with fortification approach against several relentless ailments counting cancer. As per sundry investigations reports, the naturally occurring bioactive compounds possess an unprecedented molecular diversity with the potential to modulate several metabolic processes with high priority objectives such as low toxicity, targeting multiple drug resistance and heterogeneity of the tumor cells. These attributes with bioactive compounds can provide safe and high quality of healthy life achievable with easily available low-cost alternatives and nominal or no side effects. In topical quondam, numerous potent phytochemicals and marine molecules have been isolated, exemplified, identified, and are under disparate phases of clinical trials for human welfare. In this context, the chapter addresses recently discovered plant and marine originated natural compounds for cancer therapeutics concerning with more targeted and innoxious approach with future outlook. Moreover, an attempt to consolidate data on various bioactive compounds has been made which herald to aid in unrelenting research into potential use either solely or in combination with other widely employed therapies.

Keywords: Anticancer therapeutics, Bioactive compounds, Cytotoxic, Phytochemicals, Tumorigenesis.

INTRODUCTION

CANCER is the second significant leading cause of mortality worldwide giving rise to an immense burden on communal health and is reflected to be one of the

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major challenges of the century, allied with severe medical connotation in concert with social and economic impacts [1 - 6]. World Health Organization projects 100 million cancer cases per year, causing 6 million deaths all around the world. According to them, if the trend continues, there will be a high probability of a boost in cancer cases (up to 60%) in the coming two decades.

Cancer is an uncontrolled proliferation of cells which invade other parts of the body causing acute damage at the molecular and cellular levels [3]. Moreover, it also stimulates chronic inflammation which accelerates consequences like apoptosis evasion, metastasis, angiogenesis and DNA damage [8 - 10]. The standard therapies used for cancer treatment confer lifelong morbidities along with other issues like bystander effects, multi-drug resistance, untimely relapses, low efficacy, are expensive and have several other lethal side effects [1, 2, 9, 11 - 14].

Therefore, there is an imperative need for devising castigating therapeutic interventions with broad exploration and novel health promising strategies comprising of naturally occurring bioactive compounds.

Biologically active natural compounds are used in about 80% of licensed chemotherapeutic drugs and more than half of all primary drugs. These are also responsible for curing 87% of human illnesses, including various types of malignancies [15, 16]. Natural products and their derivatives act on the life-threatening disease by interfering with the mechanism of carcinogenesis and its multistep progression, preventing proliferation by one or more pathways. The prime mechanisms of anticancer properties of bioactive compounds include; arresting cell cycle modulating processes, inhibiting metastasis [15, 16], inducing apoptosis, cleaving DNA [17, 18], permeabilizing mitochondrial membrane [11] and inhibiting angiogenesis [15], *etc*.

Many natural bioactive products derived from plant, marine and microbial sources have the potentiality to serve as chemotherapeutic as well as chemo-preventive agents [6, 10]. The phytochemicals from therapeutic plants have been employed in traditional medicines for centuries and have been the subject of scientific drug discovery even in present times. Although, the bioactives from marine sources seem as a newer dimension of study, being exploited since 1970s, but hold auspicious sources, as their chemical ingenuity and diversity outweigh terrestrial founts [17]. These pharmacologically active bioactive compounds are either refined into medicament directly or serve as “pharmacophores” for the chemical production of cognates with enhanced potencies and physicochemical attributes [19].

Plants Derived Bioactive Compounds

Among enormous miscellany of functional bioactive compounds or phytochemicals have engrossed broad recognition for their extensive anticancer bioactivities linked with antioxidant and immune-stimulating applications impacting health and wellness. Major therapeutic properties of bioactive compounds are demonstrated in Fig. (**4**). Numerous findings have highlighted that therapeutic plant derived compounds can augment the effectiveness of various cancer remedial treatments and in some cases, alleviate many of the detrimental concomitants of chemotherapeutic agents. Some of the significant bioactive compounds with prospective use in malignant therapeutics are described in the following text.

Curcumin

A polyphenolic metabolite (Fig. **1**) isolated from the rhizome of *Curcuma longa*, *C. zedoaria* and *Acorus calamus L.*(Zingiberaceae) which is accredited to broad spectrum of pharmacological activities such as antioxidant, chemotherapeutic, chemopreventive, and chemo-sensitizing pursuits [5, 20 - 25]. Antiproliferative properties of Curcumin have been demonstrated in *in vivo* and *in vitro* models against breast, pancreatic, prostate, colorectal, ovarian, skin and blood cancer, hematological malignancies and esophageal squamous cell carcinoma (EC1, KYSE450, EC9706, TE13cell lines) [5, 20, 25]. It pertains various anti-cancer attributes like: inhibiting associated enzymes such as Cyclooxygenase (COX)-2, 5-LOX and iNOS. Other anti-cancer mechanisms include caspase activation, cytochrome P450 enzymes modulation, upregulation of CDKIs, cell cycle arrest at G1, S-phase and G2/M phase check points, inhibition of NF-κB transcription factor and down-regulation of vascular endothelial growth factor's expressions, platelet- derived growth factor and fibroblast growth factors [23, 24]. Although, Curcumin plays an important role as chemo-sensitizer with some anti-tumor drugs like 5-fluorouracil, gemcitabine, paclitaxel, doxorubicin and also work as synergist with natural drugs like honokiol, resveratrol, epigallocatechin-3-gallate, omega-3 and licochalcone but the studied metabolite has exceptionally low absorptivity, demonstrates meager systemic bioavailability and is indecently metabolized [23].

Camptothecin

Quinolone alkaloids (Fig. **1**) are extracted from *Camptotheca acuminata*, a Chinese ornamental plant. The complex and its derivatives possess antineoplastic properties [1, 5, 26] linking with DNA topoisomerase 1 and inhibiting DNA's relegation and cleavage, thus leading to DNA sever and cytotoxicity [5, 26]. At present, topotecan and irinotecan, the two well-known derivatives of

CHAPTER 3

Natural Bio-actives Acting Against Clinically Important Bacterial Biofilms

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Abstract: Biofilm research is growing rapidly due to the widespread existence of biofilms in pathogens and their resistance to a variety of antimicrobial therapies. World Health Organization in 2017 categorised pathogens into three categories based on their AMR [Antimicrobial resistance] and severity of infection *viz*. critical, high and medium. *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and organisms belonging to *Enterobacteriaceae* family are top priority pathogens- 'critical', amongst which the majority of them are reported to cause the infection due to biofilm formation. As antibiotic resistance has increased tremendously in the last few years, the current research is concentrated on the development of effective approaches to inhibit biofilm formation by bacteria. Anti-biofilm activity is mediated by a spectrum of molecules obtained from plants, mammals, fungi, microbes, and marine sponges. The chapter gives a comprehensive idea about natural bioactives from plant and other sources that act as anti-biofilm agents. Clinical validation of these bioactives will aid the medical field with alternate preventive and treatment methods against pathogenic biofilms.

Keywords: Anti-biofilm agents, Antibiotic resistance, *Acinetobacter baumannii*, Bioactives, *Enterobacteriaceae*, *Pseudomonas aeruginosa*.

INTRODUCTION

A product that exhibits biological activity is termed as bioactive. These active products exert either positive or negative biological effects based on the nature of the substance, the dosage or the bioavailability [1]. Bioactive compounds have the potential to affect metabolic processes and perform functions like receptor suppression, inhibition or enzyme activation, and also involved in gene induction and suppression [2]. Bioactive compounds are important for human well-being due to their various biochemical activities, involving antioxidant, anticarcinogenic, antimutagenic, antiallergenic, anti-inflammatory, and antimi-

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crobial activities, as well as the reduction in cardiovascular disease risk factors [3 - 5].

Solid-liquid extraction using organic solvents and other methods, such as supercritical fluid extraction, high-pressure procedures, microwave or ultrasound-aided extraction and subcritical water extraction, are some commonly used methods for extracting bioactive compounds from their natural sources [4, 6 - 9]. There can be multiple sources of bioactives like plants, animal, bacteria, marine sponges, algae, fungi, *etc.* of which plants are most commonly and widely explored for their bioactives due to their strong phytochemical profile. There is a wide range of bioactive applications. However, their potential in eradicating biofilms of clinically challenging pathogens is currently under investigation.

By carrying the microscopic analysis of mucus and lung tissue in chronically compromised cystic fibrosis patients, Hoiby discovered aggregates of *Pseudomonas aeruginosa* cells and termed it as "biofilm infection." Nickel *et al.* introduced the word "biofilm" to medicine and medical microbiology in 1985. Microbial biofilms were described by Niels Hoiby as "a clump or cluster of microbes which is surrounded by an extracellular self-generated polymer matrix" [10]. The persistence of these microbial biofilms has caused severe damages to food processing industries and is considered as major obstacle in clinical treatments of chronic infections.

Biofilms are microbes extracellular secretions made up mostly of polymeric substances such as polysaccharides, proteins, and DNA. The organisms in the core of these biofilms decrease their metabolic activities acquiring a dormant state, making them more tolerant to antibiotics. Bacteria within biofilms gain resistance to antibiotics by a variety of mechanisms, including synthesis β lactamase, upregulating efflux pumps, and by modifying antibiotic target in bacteria [11]. The ECM (extracellular matrix) is a stubborn source of defence for bacteria against stress conditions *e.g.* physical, environmental, chemical and biological [12]. Increasing antibiotic resistance among microorganisms is currently one of the most serious threats to the health sector around the world [13]. These biofilms are also tolerant towards disinfectant chemicals as well as resistant to the body's defence system. Bacteria within biofilms are relatively more resistant than outside biofilm. Biofilms are found to be resistant to carbapenems and third-generation cephalosporins, which are known to be the best antibiotics currently available for treating multidrug-resistant bacteria. Based on the above characteristics, biofilm plays a vital role in human infections and exhibits important adaptive mechanisms making their eradication a challenging task.

In 2017, WHO categorised these pathogens according to their infection severity into three priority tiers: critical, high and medium. The critical group includes *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacteriaceae and effective therapies targeted towards their biofilms that need to be developed immediately [14]. Moreover, a recent review anticipated 10 million deaths per annum by 2050 due to antimicrobial resistance [15]. Since July 2020, the CDC (Centers for Disease Control and Prevention) has issued eight complaints of infections caused by *P. aeruginosa* in patients who had surgery or other invasive procedures in Mexico. Six of these occurred in patients undergoing surgical treatments [bariatric surgery, cosmetic surgery, cholecystectomy, and cancer treatment] at various healthcare facilities in Tijuana, Baja California, Mexico (CDC site: Health associated infections). *A. baumannii* is a bacteria that cause healthcare-associated infections (HAIs). An outbreak of *A. baumannii* infection was observed in the University Hospital of Angers in France and in that nearly 49 patients were infected with drug-resistant *A. baumannii* [16]. Antibiotic resistance in biofilm-forming organisms is usually associated with considerably higher mortality, morbidity, and economic burden [17]. As a result, antibiotic resistance and the potential to form single-species and polymicrobial biofilms limit the effectiveness of existing therapies, putting a financial strain on the healthcare system [18]. This creates an urge to discover either biofilm inhibiting or biofilm eradicating agents.

Some of the strategies currently being used to treat biofilms are enzymes that impair the biofilm matrix or compounds that inhibit bacterial communication, thereby increasing sensitivity to antibiotics, phage therapy, *etc.* While a few synthetic compounds demonstrated promise as anti-biofilm agents, but the natural compound drugs are preferable in terms of processing costs and success rates [19]. Thus, considering the advantages offered by the natural sources, they are being explored for anti-biofilm bioactives.

This chapter gives an insight into different natural bioactives (plants, animal, bacteria, fungi or marine organisms) that are reported to inhibit biofilms formation in critical priority pathogens (*Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae) listed by WHO. The chapter also discusses how the lack of clinical trials and other research gaps in the discovery and applications of natural bioactives as anti-biofilm agents has narrowed its usage while emphasizing the importance of *in vivo* and translational research.

Natural Bioactives against *Acinetobacter baumannii* Biofilms

A. baumannii is a major etiological agent of nosocomial infection. It possesses an ability to form a biofilm which aggravates its virulence and antibiotic resistance,

CHAPTER 4

Bioactive Compounds in Alternative Therapeutics against COVID-19

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Abstract: The COVID-19 pandemic has created a very difficult time for the whole world with utmost challenge and responsibility on the public health sector to provide symptomatic relief and timely treatment. This condition has stimulated immediate research on the mode of transmission and pathogenesis of the viral variants. As the composition of SARS CoV-2 is similar to SARS-CoV by more than 50%, therefore the management of COVID-19 can possibly be done by repurposing the existing drugs used to treat SARS-CoV infection. The management of SARS CoV-2 infection can be performed at the level of control, prophylaxis and treatment. Many bioactive compounds isolated from medicinal plants have been studied for efficacy in controlling COVID-19 infection by either repression of viral host cell adjunction and subsequent penetration or by repression of viral genomic replication. The bioactive compounds target specific viral or host cell molecules in order to control the spread of virus. Another prominent approach is the development of plant-based vaccines to control the COVID-19 infection and associated complications. The literature also provides evidence of some phytonutrients present in the food supplements which are responsible for increasing the antioxidant, anti-inflammatory, immuno-stimulatory and anti-viral activities in the host cells.

For the purpose of COVID prophylaxis and treatment, these phytonutrients can be administered in appropriate functional doses. The chapter is a compilation of research on SARS CoV-2 with its life cycle, pathogenesis, currently used drugs for treatment, including the synthetic ones and the medical herbs and the specific bioactive compounds found efficacious against COVID-19.

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Keywords: COVID-19, Phytomedicine, Therapeutics, Bioactive compounds, Vaccines, Food supplements.

INTRODUCTION

In December 2019, WHO (World health organization) announced a novel virus called coronavirus named as SARS-CoV-2, responsible for COVID-19 epidemics [1]. This disease has spread throughout the world with a total number of corona-impacted patients exceeding 208 million and about 4.3 million fatalities by the mid of August 2021 as per WHO.

The world has also witnessed the SARS outbreak in late 2002 and 2003 which was caused by SARS-CoV (Severe Acute Respiratory Syndrome-coronavirus) Virus. SARS CoV is not similar to the other coronavirus as it spreads through common cold. COVID-19 acute respiratory syndrome spreads *via the* respiratory route. There were about seven human coronaviruses discovered, named as CoV229E, HCoV-OC43, HCoV-NL63, HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2 [2].

As per the reports of WHO [2020], the cases of COVID-19 have been observed in all the seven continents reported in 197 countries, including China, Italy, Spain, United States, Germany, France, Iran, United Kingdom, and other Asian countries, such as South Korea, Japan, India, Thailand, and Pakistan (WHO 2021). Majority of infected cases have been reported in America, followed by Europe, South East Asia, Eastern Mediterranean, Western Pacific and Africa. According to a report of World Health Organization 2019, the first case of novel coronavirus was reported at the end of year 2019.

The mortality rates of SARS CoV and MERS CoV in the last two decades were of approximately 9.5% and 34.4%, respectively and SARS-CoV-2 (COVID-19) was declared to be third severe pandemic with country wise variable mortality rates. The immediate emergency action to control the virus transmission was to break the chain of infection by isolation of patients and social distancing along with country specific initiative of lockdowns to provide reasonable time to the researchers for the development and testing of drugs and vaccines [3].

The COVID-19 virus is a single stranded RNA virus. “Corona” is a *latin* word which means “Crown”, as the virus bear typical crown like surface spikes. The major cause of spreading of this virus could be due to contamination from some wild animals in seafood markets, and later spread from asymptomatic carrier population to healthy individuals through close contact [4].

COVID-19: Features and Characteristics

Causative Agent

The causative agent of COVID 19 is a virus known as coronavirus, which is a member of the family Coronaviridae. Alphacoronavirus (α CoV), Betacoronavirus (βCoV), Deltacoronavirus (δCoV), Gammacoronavirus (γCoV) are four genera included in the subfamily coronavirinae. From these, the α and β strains are capable of infecting only mammals, while the others infect birds but can also infect mammals [5].

The shape of coronavirus is round, but it possesses the capacity to transform itself according to environmental conditions. The outer envelope is known as a capsular membrane with glycoprotein projections (S proteins) which covers the core of virus, consisting of matrix protein enclosing the genomic RNA (+ss RNA). The positive strand RNA has 5'capped and 3' polyadenylated ends and looks identical to the 18S mRNA. The S proteins on the viral envelope help in the attachment of the virus to the host cell and it possesses the antigenic epitopes which are recognized by neutralizing antibodies. The shape of the S protein is subjected to modification to make the fusion of the virus with the host cell easier [6]. Recent studies show that membrane exopeptidase angiotensin-converting enzyme (ACE-2) works as a receptor for S protein for entering the human cell [7].

HCoV-OC43, and HCoV-HKU1 (betaCoVs) HCoV-229E, and HCoV-NL63 (alphaCoVs) are common human CoV and cause infection of upper respiratory tract in immunocompetent individuals [8]. Genomics study of coronavirus, which was isolated from some patients of Wuhan, showed 89 percent nucleotide identity with BAT SARS-like-CoVZXC21 and 82 percent with that of human SARS-CoV. Therefore, the experts from "International Committee on Taxonomy of Viruses" named this virus SARS-CoV-2, which contains 29891 nucleotides, encoding for 9860 amino acids, although its origin is completely unknown. It was only proposed that its origination is from animals and has undergone zoonotic transmission [9].

Similar to other Coronaviruses, it is sensitive to UV rays and heat, it was studied that virus has the ability to resist lower temperatures below 0^{o}C, the virus can be inactivated by different solvents like lipid solvents and also from ether (75%), peroxyacetic acid, chlorine-containing disinfectant, ethanol and chloroform except for chlorhexidine [8].

CHAPTER 5

Plant Based Bioactive Molecules in Diabetes with Their Therapeutic Mechanism

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Abstract: Plant based bioactive compounds are the secondary metabolites that are produced by them to perform their non-essential functions. They provide an ample source of nutraceuticals and therapeutics for humans. The research on these compounds is on trend these days and most of the research suggests their importance as therapeutic agents and as prophylactic agents against many diseases. Easy accessibility, and better efficacy with lesser adverse effects of bioactive compounds have made their research trending. Diabetes is the oldest known metabolic disease which requires a multimodal treatment approach for its management. The available drugs and treatment options are still unable to control the complications and economic burden faced by the patients. Many plants have been used traditionally for the management of diabetes worldwide. Now it has been well established that the plants provide a rich reservoir of bioactive compounds which have the potential to modulate various pathways involved in the regulation of blood glucose. This chapter discusses the common groups of plant derived bioactive compounds, their sources, and their mechanistic antidiabetic role.

Keywords: Bioactive compounds, Diabetes, Medicinal plants, Phytocompounds, Therapeutic potential.

INTRODUCTION

A bioactive compound is a substance which produces some biological activities when taken by an organism. They have the potential to modulate metabolic processes, which can aid in achieving better health conditions [1]. Thus, we can say that bioactive compounds of plant origin are the secondary metabolites which poses some pharmacological or toxicological effects in man and animals [2].

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Different plant based food that we consume like grains, fruits, vegetables, legumes, and seeds, all may contain numerous bioactive compounds. The bioactive compounds have been under consumption since the beginning of man's existence.

As there are many archaeological findings of remains of seeds and legumes in dental pieces of Neanderthal fossils, which proves the food intake of vegetable origin, including plants, fruits, and vegetables by them [3]. There is evidence in the historical books like in Chinese traditional medicines books and Ayurveda mentioning about the herbs and roots, and their application for medicinal use. There are still many preparations which include plants and roots which are still in use in the modern times as well [4].

With the development of analytical techniques like nuclear magnetic resonance spectrometry (NMR), chromatographic techniques like gas chromatography (GC), mass spectrometry (MS), high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LCMS) which aids in the isolation of single bioactive compound its purification, as well as its structure elucidation from plant extracts have become available [2]. Thus, we came to know about the phytochemical profiling of any plant based extract [5]. Based on their chemistry, the bioactive compounds can be classified as glycosides, carotenoids, flavonoids, saponins, alkaloids, saponins, phytosterols, polyphenols. Since vitamins and minerals elicit pharmacological effects, these can also be categorized as bioactive compounds [6].

Bioactive compounds have been implicated in numerous diseases, as disease modulator as, therapeutic agents, prophylactic medications and as nutraceutical supplement. These are known to affect various metabolic pathways and thus affecting functions of various organs and organ systems of body [7]. There is a plethora of examples which prove the therapeutic potential of bioactive compounds. Falcarinol and falcarindiol, which are bioactive compounds obtained from carrot, possess anti-inflammatory effects [8]. Some of the bioactive compounds namely, resveratrol, curcumin, catechins, *etc*. are known to have an anti-ageing effect by their ability to directly inhibit oxidizing agents like reactive oxygen species and inflammatory pathways [9]. Polyphenolic bioactive compounds can modulate the transcription factors like mitogen activated kinase, which is crucial for cell division process [9, 10]. 6-Shogaol, ginkgolide, quercetin, *etc*. have the ability to interact with various neuronal receptors, thus inducing the synthesis of neurotropic factors that promote regeneration, growth, and neuronal survival, reducing the rate of progression of neurodegenerative diseases [11]. Bioactive compounds are well known immunomodulators, as they can affect the B cells and T cells proliferation, thus they play an important role in immune related diseases and different types of cancers [12].

Diabetes mellitus (DM) can be considered as one of the oldest and most commonly known endocrine disorder, which is characterized by an elevation of the blood glucose levels that requires its frequent monitoring and proper control [5]. DM can be classified into many types, however, the most common types are type 1 and type 2 Diabetes mellitus. Type 1 DM is mainly associated with the failure of insulin production due to destruction of insulin-secreting pancreatic β-cells by cytotoxic T Cell (CD8+) mediated autoimmunity whereas, the type 2 DM is the result of insulin resistance and reduction of insulin production [5, 13]. DM in the later stages leads to complications like nephropathy, neuropathies, cardiovascular disorders and the patient becomes prone to a number of infections as well [14]. As per WHO data, a third leading cause of morbidity and mortality after heart attack and cancer is due to DM. In the year 2014, there were 8.5% of adults aged 18 and more had DM. In the year 2012, 2.2 million deaths were due to high blood glucose and in the year 2016, DM caused 6 million deaths. There was 5% increase in premature mortality from DM between the years 2000 and 2016. As per World Health organization people with DM were more prone to COVID-19 as there was 33.8% comorbidity.

The plant based bioactive compounds are known to have better efficacy, a wide availability, and fewer adverse effects which make them more in demand as compared to the synthetic medicines for the management of DM [15]. There are more than 1200 plants with known antidiabetic properties. Out of them, 400 plants have proven the antidiabetic properties after appropriate research and investigation [16]. Bioactive compounds are excellent antioxidants, for example, α and β carotene, ascorbic acid (vitamin c), lutein, lycopene, *etc*. help in managing the complications like endothelial dysfunction and atherosclerosis in the patients with DM [17]. Polyphenolic compounds and vitamin E are other essential bioactive compounds with the ameliorative potential against oxidative stress related to diabetic risk [18]. Several phytochemicals have been associated with benefits to people with DM, including cinnamaldehyde, epigallocatechin, and chlorogenic acid, showing hypoglycemic effects, α-amylase inhibitor and insulin sensitizer, respectively [19]. The available evidence from *in-vitro* and animal studies suggested the protective effects of cinnamon as an antitumor, anti-inflammatory, antioxidant, antimicrobial, and cholesterol lowering agent, as a treatment of infectious diseases, and for the prevention of cardiovascular diseases [20]. There is well-documented profile of pharmacological effects of cinnamon for the treatment of type 2 DM [21]. Moreover, the bioactive compounds can be an adjuvant and therapeutic option for multimodal treatment for managing DM due to their better safety and efficacy profiles.

CHAPTER 6

Marine Algal Bioactive Metabolites and their Pharmacological Applications

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Abstract: Thousands of bioactive components are derived from various marine macro and microalgae. Such beneficial algae are considered as a renewable and sustainable resource of bioactives with potential use as dietary food supplement, anti-viral, antiinflammatory, anti-cancerous, anti-oxidant, anti-diabetic, anti-bacterial agents which can provide nutritive and health care benefits. The biochemical infrastructure of algae comprises proteins, lipids, polysaccharides, minerals, vitamins *etc*. which can be used as nutritional and dietary sources along with use in therapeutics and cosmetics. The therapeutic and industrial applications of the algal derivatives are primarily due to the secondary metabolites such as astaxanthin, aquamin, alginates, fucoidan, omega-3-fatty acids, polyphenols, fucoxanthin, *etc*. This chapter focuses on various algae derived bioactives and their wide range of applications.

Keywords: Algae, Alginates, Aquamin, Astaxanthin, Bioactive, Fucoidan, Fucoxanthin, Polyphenols, Omega-3- fatty acids, Therapeutics.

INTRODUCTION

Algae is much familiar for their cosmopolitan distribution found anywhere in all kinds of aquatic biotypes from temperate, tropical, extremes of cold and hot regions like oceans, ponds, lakes, and wastewater due to their tremendous capability to tolerate the wide variation in physical factors. There are as many as 12,272 algae classified into red, green, blue green, and brown algae on the basis of the pigment they contain *viz* Cyanobacteria (chlorophyll-a, chlorophyll-d, chlorophyll-f, phycocyanin, phycoerythrin, phycobiliprotein), Glaucophytes (chlorophyll-a, phycobiliprotein), Phaeophyta (chlorophyll-a, chlorophyll-c, β-carotene, fucoxanthin, violaxanthin), Chlorophyta (chlorophyll-a, chlorophyll-b, β-carotene, xanthophyll), and Rhodophyta (phycocyanin, phycoerythrin, carotene,

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xanthophyll) [1]. The algae can also be classified on the basis of multicellularity (macroalgae) and unicellularity (microalgae). Both the algae are photosynthetic and aquatic but macroalgae are plant-like and can be seen by naked eyes therefore, called as seaweeds while the microalgae are smaller in size, can be seen under microscope called as phytoplankton. The seaweeds and phytoplankton's both belong to the basic tropic level (primary producers) in the marine water ecosystem. These are genetically diverse group of organisms that keep balance between the abiotic and biotic factors of oceanic life directly or indirectly [2]. These are the major source of potential minerals, vitamins, lipids, polysaccharides, sterols, proteins, fibres, macro and micronutrients [3]. The ecologist, pharmacologist, researchers and aqua culturist are now more focused on the seaweeds for their tremendous chemical composition and properties. Particularly the aqua culturist started growing the sea weeds with other animal groups to generate integrated and multitrophic groups that provide both sustainability and proper management practices [4]. New era of technological evolution leads to the use of algae in diverse branches like pharmaceuticals, cosmeceuticals, nutraceuticals, therapeutics, metabolomics, biofuel production, biofertilizer production, and generation of new medicinal group because of the presence of their ultimate and distinct bioactive components [5, 6].

The bioactive compounds are primary and secondary metabolites derived from algal sources, and can be purified and isolated by different techniques. The biochemical infrastructure of the macro and microalgae comprises the variable concentration of proteins, lipids, carbohydrates, minerals, vitamins, fatty acids, *etc.*, depending upon the type of the strain and abiotic factors they live in [7]. Microalgal proteins are used as food and food by-products due to their well-defined amino acid profiling [8]; microalgal polysaccharides are used extensively in cosmetic production and hygroscopic agents [9]; their lipids are a source of biodiesel production, nutraceuticals and infant formulation [10]; and microalgal Polyunsaturated fatty acids (PUFAs) are comparable to the fish oil and used in production of high valued commercial products [10]. Other compounds like omega 3-polyunsaturated fatty acids play therapeutic role in treating chronic inflammatory diseases [11]; their carotenoids are used as anti-inflammatory bioactive compounds [12], and sulfated polysaccharides (SPS) are extensively studied in both the macro and microalgal for anti-inflammatory activity [13].

The essential benefits of algae-based metabolites can be obtained from the primary metabolites as various types of lipids, amino acids and proteins, and different carbohydrates which are generally present in various types of algae in variable concentrations. But the specific benefits of various marine macro and microalgae are due to the unique compounds called secondary metabolites. Thousands of such secondary metabolites acting as bioactive components have

been extracted and screened for their potential properties such as anti-viral, anti-inflammatory, anti-cancerous, anti-oxidant, anti-diabetic, anti-bacterial, nutritive and health care benefits (Fig. **1**).

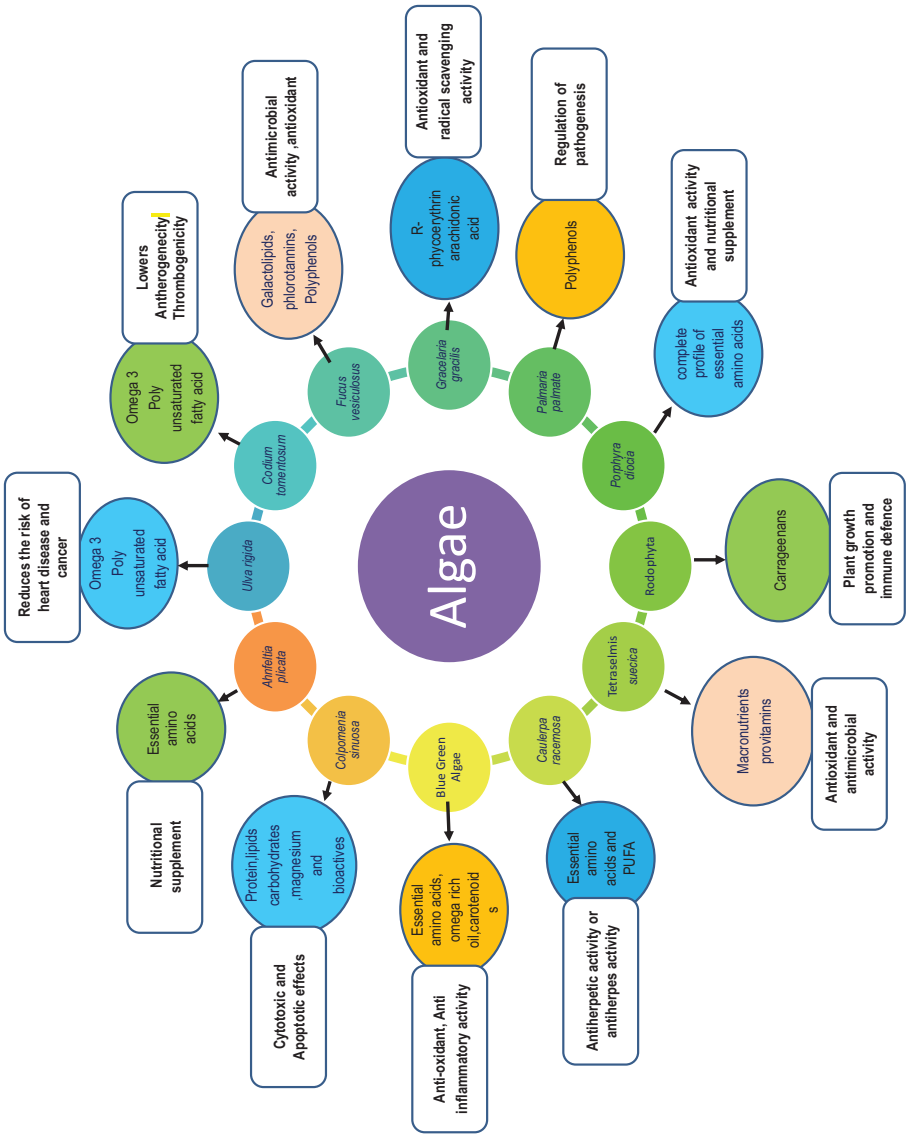

Fig. (1). Represents the Marine algae derived bioactive compounds and their potential uses.

CHAPTER 7

Nutritive Importance and Medicinal Properties of *Foeniculum vulgare* Mill. (Fennel) and *Trachyspermum ammi* L. (Ajwain)

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Abstract: In tropical and sub-tropical countries, spices have a long history in traditional food preparations. Several spices are described to have medicinal effects. Among them are *Foeniculum vulgare* Mill. and *Trachyspermum ammi* L. belonging to the Apiaceae family are the most common spices known for their highly aromatic nature and flavor with culinary and traditional uses. *F. vulgare* seeds increase urine flow, improve the digestive system, promote menstruation and improve milk flow. Various pharmacological activities of *F. vulgare* such as antioxidant, hepatoprotective, antimicrobial, estrogenic, acaricidal, antihirutism, antidiabetic, anti-inflammatory, and antithrombotic, have been reported in the literature. *T. ammi* seeds are used for relieving flatulence, dyspepsia, spasmodic disorders, common cold, acute pharyngitis, sore and congested throat, dipsomania, and hysteria. *T. ammi* seeds are reported to possess antimicrobial, antioxidant, hepatoprotective, nematicidal, antihelmintic, and gastroprotective activities. The review presents an overview of the traditional uses, phytochemical constituents, and pharmacological properties of *F. vulgare* and *T. ammi* seeds.

Keywords: *Foeniculum vulgare* Mill, *Trachyspermum ammi* L, Phytochemical constituents, Anethole, Thymol, Apiaceae family, Estrogenic activity, Antioxidant, Acaricidal, Antibacterial, Antihirutism, Hepatoprotective, Anti-inflammatory, Antifungal, Antithrombotic, Antidiabetic, Antihypertensive, Antilithiasis, Nematicidal, Ameliorative, Antitussive.

INTRODUCTION

Spices are often assumed to be safe based on their traditional use for a long period. As estimated by the World Health Organization, about 80% population of developing countries depends on plant-derived drugs for their primary health care needs [1, 2]. *Foeniculum vulgare* Mill (Fig. **1a**) and *Trachyspermum ammi* L.

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seeds (Fig. **1b**) are the commonly used spices known for their beneficial effects on humans and animals.

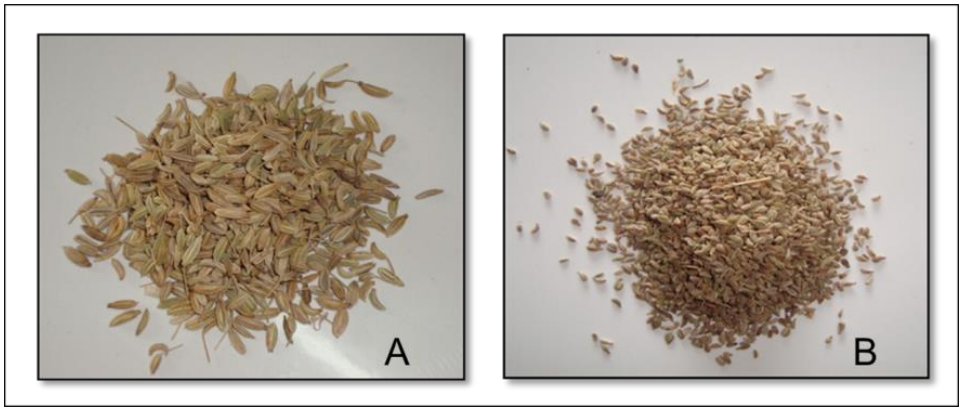

Fig. (1). a.*Foeniculum vulgare* Mill (Fennel) seeds and **b.** *Trachyspermumammi*L. (Ajwain) seeds.

Foeniculum vulgare Mill or *F. vulgare* (Apiaceae family; Table **1**), commonly known as fennel, is one of the widespread perennials or an annual herb having feathery leaves, yellow flowers, and aromatic odor. Earlier, the Mediterranean region and Southern Europe were native places of *F. vulgare,* but the plant is widely cultivated in the tropical and temperate regions of the world. The plant is about 2.5 m tall with hollow stems [3]. The fruit is a dry seed of 4–10 mm in length containing phenolic glycosides, flavonoids, phytosterols, triterpenes, saponins, and volatile oils (thymol, trans-anethole, fenchone, carvacrol, terpinene, P-thymene and thymol methyl ether) [4]. Fennel seeds are highly aromatic in nature and used as a flavor enhancer in baked foods, ice cream, alcoholic liqueurs, and herbal preparations [5]. Fresh and dried seeds of *F. vulgare* are brown/green in color which gradually turns to grey on the aging of the seeds. Green seeds are best known for cooking. In Kashmiri Pandit and Gujarati cooking, fennel is the most important spice used [6].

Table 1. Bentham and Hooker system of classification of fennel and ajwain.

-	Fennel	Ajwain
Kingdom	*Plantae*	*Plantae*
Subkingdom	*Tracheobionta*	*Tracheobionta*
Superdivision	*Spermatophyta*	*Spermatophyta*
Division	*Magnoliophyta*	*Magnoliophyta*
Class	*Magnoliopsida*	*Magnoliopsida*

(Table 1) cont.....

-	Fennel	Ajwain
Subclass	*Rosidae*	*Rosidae*
Order	*Apiales*	*Apiales*
Family	*Apiaceae*	*Apiaceae*
Genus	*Foeniculum*	*Trachyspermum*
Species	*Foeniculum vulgare* Mill	*Trachyspermum ammi* L.

Trachyspermum ammi L. or *T. ammi* (Apiaceae family; Table **1**), commonly known as Ajwain is a 60-90 cm tall, profusely branched annual herb a native of Egypt. The seeds are cultivated in Iran, Iraq, Pakistan, Afghanistan, and India. In India, Gujarat, Madhya Pradesh, Uttar Pradesh, Maharashtra, Rajasthan, Bihar, and West Bengal are the regions where *T. ammi* is grown [7]. Various phytochemical constituents are reported to be present in *T. ammi* seeds *viz.* glycosides, carbohydrates, phenolic compounds, saponins, volatile oil (γ-terpinene, thymol, para-cymene, and α- and β-pinene), fats, protein, fiber and mineral substance containing phosphorous, calcium, iron and nicotinic acid [8]. It is regarded as a traditionally potential herb known for its curative properties in humans and animals [9]. In the Indian system of medicine, *T. ammi* seeds are administered for various stomach disorders in which a hot and dry fomentation of the seeds is lapped on the chest to cure asthma and a paste of powdered seeds is applied externally for decreasing colic pains [10]. Ajwain-ka-arak (aqueous extract of the seeds) is a popular preparation for diarrhea [11]. *T. ammi* seeds are therapeutically used as stomachic, carminative, expectorant, antiseptic, amoebiasis, and antimicrobial agents. Seeds are also known to prevent abdominal tumors, abdominal pains, and piles [12]. Many ajwain ayurvedic formulations are available which are given to overcome infections with worms [8]. Seeds are also used for relieving flatulence, dyspepsia, spasmodic disorders, common cold, acute pharyngitis, sore and congested throat, dipsomania, and hysteria [13].

The review aims to present the reported knowledge of phytochemical composition, culinary uses, and pharmacological studies of plant-derived extracts of fennel and ajwain seeds.

Phytochemistry of *F. vulgare* and *T. ammi*

F. vulgare seeds have been reported to possess moisture (6.3%), proteins (9.5%), fats (10%), minerals (13.4%), fibers (18.5%), and carbohydrates (42.3%). The minerals such as potassium, calcium, iron, sodium, phosphorus, and vitamins *viz.* riboflavin, thiamine, vitamin C and niacin are also present [14]. Pasirija *et al.* studied that *F. vulgare* seeds constitute 8% volatile oil (about 10-15% fenchone, 50-60%, anethole, and 2-9% estragole and methylchavicol) flavonoids, coumarins

CHAPTER 8

New Insights into Biological and Pharmaceutical Properties of Bioactive Compounds in Various Diseases of Farm Animals

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Abstract: Farm animals have a crucial role in producing sources of protein and other nutritive products for humans. However, these animals are confronting diverse challenging ailments and subsequent oxidative stress, which reduces the efficiency of production and impairs animal welfare. Bioactive compounds obtained from plants and other natural provenances have now been accredited as the crucial steppingstone against the numerous persistent diseases encountered by farm animals. Bioactive compounds possess remarkable molecular diversity and modulate numerous metabolic processes with high precedence goals, low toxicity, exhibiting high efficacy with low cost, easy availability with less or no side effects.

In this context, the chapter addresses recently observed bioactive compounds for the treatment of various livestock diseases. Moreover, an attempt to consolidate information on numerous bioactive compounds has been made which brings aid in unrelenting research into potential use.

Keywords: Bioactive compounds, Coccidiosis, Livestock disease, Phytochemicals, Poultry.

INTRODUCTION

Livestock animals play a crucial role in the economic and socio-cultural lifestyle population residing in developing and developed countries' rural and urban areas. These contribute to the food supply, source of earning, source of employment, and sustainable agriculture production [1]. Animal waste is used to manure soil and as a source of biofuel. Farm animals and their products are an economical source of high-quality protein and another energy source for human consumption. Thus, the

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well-being of livestock seems essential for an uninterrupted supply of aforesaid benefits which can be achieved through good husbandry and proper hygiene.

The production of farm animals has been challenged by environmental issues and consumers´ attitudes as well as diseases. Farm animals are prone to some diseases, such as foot and mouth disease that affect all cloven-footed animals, Coccidiosis which affects poultry animals, Anthrax, and various other diseases caused by protozoans, bacteria, and other parasites [2 - 4].

A range of feed additives such as antibiotics, phytobiotics, probiotics, and prebiotics have been used to improve the health and production of farm animals. The livestock production system and welfare standards are continuously changing for farm animals. Their production in developed countries relies on several synthetic compounds to maintain the health of animals and to increase production. However, a few terrible consequences and outcomes of these practices are rising, so there is a requirement of some natural alternative methods to cope with healthy animal production [5].

In livestock, antibiotics are used as therapeutic agents to treat disease. The excessive use of these antibiotics has led to an increase in antibiotic resistance in pathogens. Therefore, there is an imperative need for devising castigating interventions with broad exploration and novel health promising strategies comprising naturally occurring bioactive compounds. Bioactive compounds extracted from plants and other sources can be a milestone in farm animal management [6 - 9].

There is worldwide interest in utilizing the bioactive properties of plants as a less costly, easily available alternative to chemical and synthetic food products and drugs. Medicinal plants have been exploited by developing countries for centuries to treat animals. Various medicinal plants from traditional phytotherapy are used for animal health care and food supplements. These supplements are also referred to as phytobiotics or phytogenics, which are derived from plants and are incorporated into animal feed and medicines to increase the immunity and productivity of animals [6]. Plant secondary metabolites (*e.g.* tannins, essential oils, and saponins) have the ability to manipulate rumen fermentation to improve the ruminant production system and also provide health benefits to livestock [2, 4].

Marine-derived bioactive compounds, on the other hand, are a subset, having only been exploited since the 1970s, but hold an auspicious source, as their chemical ingenuity and diversity outweigh that of terrestrial founts [10]. Marine weeds, sponges, and other organisms have also been reported as potential bioactive compounds containing sources. These bioactive compounds isolated from marine

sources exhibit various bioactivities such as antimicrobial, anti-inflammatory, and antioxidative effects on humans, aquaculture, and veterinary commodities (*e.g.* cattle and poultry farming) [7 - 9].

Plant-based Bioactive Compound for the Treatment of Livestock Diseases and their Mechanism of Action

Among an enormous miscellany of functional bioactive compounds, phytochemicals have engrossed broad recognition for their extensive bioactivities linked with antioxidant and immune-stimulating applications impacting health and wellness. Numerous findings have highlighted that therapeutic plant-derived compounds can augment the effectiveness of various farm animal disease remedial treatments. Some of the significant bioactive compounds with prospective use in the treatment of livestock diseases are described in the following text:

Natural Phenolic Compounds

These are the bioactive compounds that are derived from secondary metabolites of plant tissue [11]. They are classified based on carbon chain length, side groups, distribution in nature, and part of the plant from which they are derived [12]. Herbs, vegetables, and spices have abundant phenolic compounds [13, 14]. These compounds have the capability to control oxidative stress in animal cells and act as an immune booster. In the remnants, polyphenols perform the following role:

a. Interact with rumen microbiota, affecting various biochemical processes such as protein degradation, lipid metabolism, and carbohydrate fermentation. Inhibitory effects of these compounds have also been reported on some fibrolytic bacteria and protozoa [12, 15].
b. Enhance the production of livestock products such as meat production [12].

Few phenolic compounds with their uses in the treatment of livestock are mentioned in the following text:-

Tannins

Tannins are defined as polyphenolic compounds. Tannins exist in fruits (*e.g.* berries, pears, and apples), foraged legumes, nuts, *etc* [16, 17]. The antimicrobial effects of tannins in chicken have been reported by various investigators. One of the most common parasitic ailments in poultry farm animals is coccidiosis, which is induced by *Eimeria* species of protozoan family [18]. Coccidiosis can result in reduced growth, and cause various digestive disorders and oxidative stress [19]. Tannins (hydrolyzable tannins, condensed tannins) and their derivatives with

CHAPTER 9

Bioactive Constituents and Anti-diabetic Activity of the Indian Medicinal Plant *Hemidesmus indicus* R. Br.: An Overview

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Abstract: *Hemidesmus indicus* R. Br. is a laticiferous, slender, and twining shrub, which is found over almost every part of India. Its roots (*Anantmul* - Sanskrit meaning: endless root) are particularly used extensively as a single drug and in formulations with other plants to treat several ailments. In view of the wide range of medicinal properties claimed in traditional medicine, significant efforts have been made to determine the efficacy of *Hemidesmus indicus* through pharmacological experiments *in vitro* and *in vivo* models. These include analgesic, anti-inflammatory, antipyretic, antioxidant, antiarthritic, hepatoprotective, antiepileptic, anticonvulsant, antiulcer, antivenom, antiacne, and antipsychotic activities. Recent studies have also established anti-diabetic, anti-carcinogenic, anti-venom, and wound healing activities. Extensive phytochemical investigations have been carried out by several research groups. The present review provides an overview of the bioactive compounds of this Indian medicinal plant. Several classes of compounds, *viz*. triterpenoids, steroids, steroid glycosides, coumarin-lignoids, flavonoids in addition to many simpler compounds, have been isolated and characterised from different parts of *H. indicus*. These are listed, along with brief write-ups on isolation procedures, spectroscopical and chemical characterization, and their biological properties. Particular emphasis is given to the anti-diabetic properties associated with it, *indicus* root extracts, and the factors contributing to these properties.

Keywords: Anti-diabetic, Ayurvedic drugs, Coumarino-lignoids, *Hemidesmus indicus*, Indian sarsaparilla, Phytochemistry, Terpenoids, Volatile constituents.

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INTRODUCTION

Hemidesmus indicus R. Br. (Fam. Periplocaceae), also known as Indian sarsaparilla, is one of the important medicinal plants in the Indian Ayurvedic system [1 - 14]. It also finds use in the Siddha and Unani schools of traditional medicine. *H. indicus* R. Br. (*Sariva*, *Anantamul*, Indian *sarsaparilla*) (Fig. **1**) is a slender, laticiferous, and twining shrub, that grows throughout India. It grows wild and is also common in hedges. Its root bark and roots are extensively used in the Indian traditional healthcare system. Some of its vernacular names are *Anantamul*- Bengali, Hindi, Punjabi, Marathi; *Onontomulo*, *Suguddimalo*- Odiya; Sariva, Swet-sariva - Sanskrit; *Sugandhipala* - Telugu; *Namdaberu*, *Sogadaberu*- Kannada; *Nannari* - Tamil, Malayalam, Gujrati; *Zaiyana* – Arabic; *Ushbanidi* - Persian.

Fig. (1). *Hemidesmus indicus*cultivated in flower-pot at CARI.

The use of *H. indicus* in various traditional and ethnomedical practices [2 - 6] is recorded in different states in India - Bengal, Odisha, Madhya Pradesh, Assam, Goa, Uttar Pradesh, Gujarat, Kerala, Maharashtra, Karnataka, Andhra, Tamilnadu and Telangana. The plant is also found in local schools of traditional medicine in Iran (Persia), Pakistan, Bangladesh, and the Arabic Middle East. Its roots and root bark (*Anantmul* - Sanskrit literally meaning: endless root) are used extensively as a single drug and in formulations with other plants to treat several ailments. It has been reported that *Anantamul* is used as an ingredient in nearly 46 Ayurvedic preparations, as single or in combination with other drugs [10]. *H. indicus*, which was formerly under the family Asclepiadaceae, has been now placed in Periplocaceae family on the basis of the pollinical characters [6]. Genetic fingerprinting has also been used to identify this plant [6]. However, several recent publications still continue to place the plant under Asclepiadaceae.

Detailed phytopharmacognostic studies have already been carried out on the roots of *Anatamul* [15]. *H. indicus* is distinguished by its brown slender, sparsely branched, rigid, tortuous, elongated, cylindrical roots with the rough and wavy

outer surface, externally dark tortuous with transversely cracked and longitudinally fissured bark, and internally as yellowish-brown. Rootlets are thin and wiry, the cork is thin and separates easily, peeling off in flakes. Its root and root bark possess a pleasant mild aroma. The leaves are opposite to one another, firm, shiny and smooth varying in shape and size according to age. Flowers are small in size, green externally and deep purple internally.

The therapeutic properties of Sariva summed up in a Sanskrit *sloka*, is quoted in the Treatise of Indian Medicinal Plants, Vol. 4 [2]. It is mentioned that this plant is snigdha (cool), svādu (sweet), spermatopoietic, anti-dyspnoeic, dyspepsia, anorexia, cough, cures vitiated tridosha, fever menorrhagia and diarrhoea, invigorating diuretic and rejuvenating; a remedy for rheumatoid arthritis, skin diseases, gout and gonorrhea and mercury poisoning [2]. The source books [2, 3] also report that root and root-bark of *H. indicus* are diaphoretic, demulcent, diuretic which can be prescribed in fever, chronic cough, anorexia, leucorrhoea, dyspepsia, skin disease, chronic rheumatism and ulcerations, constitutional debility, kidney trouble, and diarrhea.

Other pharmacological properties reported on *H. indicus* include analgesic, antioxidant, antiarthritic, anti-inflammatory, antipyretic, anticonvulsant, hepatoprotective, antiepileptic, cytotoxic, antiulcer, antiacne, antipsychotic activities, antibacterial, antinociceptive, *etc*.

Roots of *H. indicus* are used to cure various skin diseases, anorectal diseases asthma, dysentery, bronchitis, leucorrhoea, syphilis, paralysis and various types of urinary disorders. Recent studies have also established anti-diabetic, anti-cancer, anti-snake venom and wound-healing activities [2 - 14]. In view of the wide range of medicinal properties claimed in traditional medicine, considerable efforts have been made to establish the efficacy of *H. indicus* through pharmacological studies both *in vitro* and *in vivo* models. The growing demand of Anantamool, in view of its widespread use, is resulting in heavy strain on the existing resources causing and depleting its supplies; in fact, its very existence may become endangered. Substitutes and adulterants often used are roots of the following four species- *Cryptolepis buchanani* Roem and Schult., *Decalepis hamiltonii* Wight, *Ichnocarpus frutescens* R. Br., and Arn and *Utleria salicifolia* Bedd. ex Hook. f [6].

Anantamul, introduced to the European healthcare system in 1831 [16], is now receiving attention as an Ayurvedic product in Europe as well as the USA. Weissner in a review entitled ‘Anantamul, a review of biomedical studies and US products’ [17] has given a useful overview of the usage of this drug in the USA in recent times. She also pointed out the lacunae of available data on it, which limits

CHAPTER 10

Utilization of Tea Polyphenols Against Pesticide Induced Toxicity: International and National Scenario

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Abstract: Exposure to pesticides has become a major toxic threat to human and non-target species in India due to the extensive use of chemical-based pesticides in agriculture and for public health purposes. Pesticide induced DNA damage is caused by exposure to certain carcinogenic pesticides through DNA adduct formation and generating altered cells, and subsequently leading to health hazards including cancer. Bio-pesticides are available to prevent the menace of pesticides on human health, such as integrated pest management, use of personal protective measures, or use of non-chemical. Being an agrarian country and its sole dependency on agriculture sectors for most rural employment, India continues to expect its dependency on chemical pesticides, as evident from the high annual demand for pesticides. Therefore, there is an urgent need for an effective approach to reduce the harmful impacts of unavoidable human encounters with toxic pesticides. In this endeavor, preventive measures in the form of functional foods and dietary antioxidants could be employed as one of the complementary and alternative therapeutic approaches to counteract against the ill effects of pesticides in humans. In the past, tea polyphenols have demonstrated an excellent ability to reduce toxicant-induced cellular damage, and DNA damage through mutations, apoptosis, and cancer. In the present review, we have summarized the research carried out on the use of tea polyphenols to counter pesticide toxicity so far and discussed it further from the viewpoint of International and national importance.

Keywords: Bioavailability, DNA damage, Genotoxicity, Nano-formulations, Pesticides, Polyphenols.

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INTRODUCTION

Pollution from environmental mutagens, such as chemical pesticides, is an increasing concern. Many times, adverse impacts on the environment as well as on non-target species dominate the favourable consequences of pesticide use. Agricultural workers and their family members are at high risk of pesticide-induced DNA damage, which prolongs many disease conditions or even death in countries like India. An effective and sustainable method to reduce the adverse impact of pesticide use on health is highly demanded.

There is a high demand for pesticides in India. Most of these pesticides have a residual effect on the environment and human body, leading to many complications. DNA damage in the human body is a molecular marker indicative of pesticide exposure and can be informative in pesticide management through biomonitoring. The biomonitoring DNA damage in pesticide-exposed people is necessary for managing the health issues caused.

Being an agrarian country, there is a high demand for chemical pesticides in India. Out of 234 registered pesticides in India, includes WHO classified Class Ia (4), Class Ib (15), and Class II (76) represent about 40 percent of the registered pesticides in India.

Several of these pesticides have a residual effect on the environment and human body, leading to many short-term and long-term complications. Effective therapeutic agents are required in this endeavor to protect against pesticide-induced DNA damage and for biomonitoring purposes in farmers, thereby preventing further development of complications such as cancers. Tea polyphenols have been studied for their excellent ability as a protective antioxidant agent against many cancers and other diseases in laboratory conditions indicating their potential use as an alternative therapy. The use of tea polyphenols can be an effective and sustainable method to reduce the effect of pesticides on human health. Here, in the present review, we emphasized the role of tea polyphenols against pesticide-induced toxicity at both the national and international levels.

International Scenario

Pesticides are the substances or mixtures of substances having agricultural utility to protect crops from pests, weeds, and diseases as well as in public health for use against diseases like malaria, dengue, and schistosomiasis, mostly vector-borne diseases. Several pesticides that adversely affect human and environmental health are banned for their use in agriculture [1]. In a rural area, the agricultural workers and residents are often exposed to toxic pesticides and thus are at high risk of

pesticide toxicity. The type, duration, route, and health condition of the exposed individual are the main factors in imparting toxicity of the pesticide. After encountering a pesticide, it may be metabolized in the body, excreted, stored, or bioaccumulated [2].

Various adverse effects were found to be linked to the toxic nature of pesticides. Several health effects such as diseases of the skin, GI, respiratory, endocrine, reproductive, neurological as well as carcinogenic effects were seen as health hazards of pesticides in the exposed population [3 - 5]. Pesticide exposure in any form accidental, occupational, or intentional, may lead to severe health hazards, including death [6]. World Health Organization has estimated about 500,000-1,000,000 people as victims of pesticide poisoning every year around the world; of these two third belong to developing countries [7].

One of the main mechanisms of chronic and severe pesticide toxicity is oxidative stress induced by several pathways such as free radical overproduction, modification of antioxidant defense system, or detoxification and scavenging enzymes [8]. Various pesticides, such as organochlorines, organophosphates, carbamates, and pyrethroids, are known to induce toxicity mainly through oxidative stress [9 - 11].

Free radical production through increased oxidative stress damages cellular structures and molecules like DNA, RNA, and proteins disrupting the normal cellular process. When the capacity of the body to neutralize or repair such damage is overwhelmed, damaged molecules accumulate and disrupt normal cellular processes. In the long run, as seen with chronic exposure to pesticides, these disruptions lead to several diseases, including neurodegenerative diseases, congenital anomalies, and cancers [12]. Pesticides or their metabolites-induced toxicity involves various processes which can cause direct damage to DNA or induce single-strand DNA breaks employing DNA excision, replication, and recombination or apoptosis [13]. Damages to DNA can be considered markers for the onset of cancer risk; therefore, reducing DNA damage as an initial event of the carcinogenesis process must have significance in reducing the risk of cancer [14].

Therefore, many studies, are focused on pesticide-induced DNA strand breaks, chromosomal aberrations (CA), micronuclei (MN), sister chromatid exchange (SCE), as well as epigenetic modifications [15 - 20]. Due to chronic exposure to pesticides, epigenetic alterations occur, which are known to interfere with gene expression that took place without any modification of DNA sequence [21]. In South Brazil, soybean farmers showed increased values of DNA damage due to chronic exposure to multiple pesticides; this persistent genetic instability due to hypermethylation of DNA may be held responsible for the critical events in the

CHAPTER 11

Therapeutically Important Bioactive Compounds Derived from Fungal Origin

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Abstract: The rising of chronic ailments impinged on humans worldwide has paved the urgent need for newer therapeutic vital compounds that are biologically active and have the capacity to endeavour without exerting any adverse or cytotoxic effects. This necessitates extensive research to investigate unexplored natural sources for such promising sources. A diverse array of fungi species has garnered considerable attention over the past century due to the assortment of their opportunities to generate novel active ingredients with multifunction mechanisms towards recuperative applications. Some of the fungal bioactive compounds possess exclusive therapeutic potential and pharmaceutical importance. These efficacious bioactive compounds including Paclitaxel, Podophyllotoxin, Enniatins, Camptothecin, Ascophytatin with their properties like anti-bacterial, antiviral, anti-parasitic, anti-diabetic, anti-cancerous, immunomodulatory are discussed in this chapter.

Keywords: Endophytes, Topoisomerase, Karyokinetics, Anti malignant, Paclitaxel , Podophyllotoxin, Enniatins, Camptothecin, Ascophytatin.

INTRODUCTION

From the dawn of time, nature has played a significant role in pharmaceutical research for humankind by offering therapeutic medications. The exploration of natural products has a lot of untapped potential, and several pieces of research have emphasized the considerable benefits of the same in the development process. The use of natural compounds is also considered a revolutionary development in the study and application of chemical complexes from biological origins with new curative capacities to achieve complex objectives of disease control [1, 2].

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Additionally, there has been a substantial shift in the current scenario to a more sustainable, environmental, and green lifestyle due to the emergence of contemporary diseases as well as the encroachment of drug-resistant pathogens escalating tremendously and rendering the existing antimicrobial medicines ineffectual [3, 4].

However, an extensive investigation for better and more effective agents to cope with these health issues is indeed ongoing and microorganisms offer a unique source of impending compliant chemicals. These are endowed with an excellent opportunity to get a constant supply of biologically active metabolites in order to serve the needs of development with safety research and/or industrial output [5, 6].

The research on bioactive compounds of fungal origin has found importance since the discovery of penicillin in the 1930s. Fungi have become a dominant contributor to pharmaceutical drugs that helps in generating life-saving medications such as antibiotics, antiparasitic, antibacterial, antifungal, antioxidant, immunosuppressant, antiviral, anti-inflammatory, anticancer, and cholesterol-lowering compounds. This has raised scientists' awareness of bioactive compounds produced by fungus in the rhizosphere or floral endosphere that might be utilized for a spectrum of activities versus human infections [4, 7 - 9].

Moreover, fungi are one of the greatest resources among living organisms from land and marine sources that have been exploited by humans since prehistoric times as these tend to play a critical role in economic and environmental balances. These have a unique metabolism that encourages and promotes a plethora of functional metabolites with a variety of chemical configurations of diverse classes allied with phenylpropanoids, terpenes, polyketides, alkaloids, *etc* [10].

Furthermore, medicinal herbs are the abode of a wide range of microbial domains. Their reliance on the biosynthesis of bioactive metabolites as a remedy to combat the rise of new drug-resistant infections has heightened the search for a non-chemosynthetic substitute to treat human illnesses. According to studies, just 7% of the 1.5 million fungal species have been discovered; despite new results utilizing next-generation sequencing reveal that there are between 3.5 and 5.1 million fungal species on the planet. As a result, fungal endophytes have taken over the environment and might be a viable source of many bioactive compounds [8].

As per studies, about 18 percent of plant-derived molecules can also be generated by their related fungus. Taxol, for example, is a bioactive chemical produced from the medicinal plant Taxus and the endophytic fungus *Taxomyces andreanae*. As a

result, the Taxol from *T. andreanae* has a distinct advantage over its host plant in terms of fermentation and biosynthesis [8].

The present chapter deals with major bioactive compounds derived from various endophytic or non-endophytic fungal strains with established therapeutic potential. These varieties can be used for the mass production of bioactives for pharmacological uses.

Important Fungal Bioactive Constituents with their Therapeutic Uses

Podophyllotoxin [C22H22O8]

A non alkaloid, lignan metabolite (Fig. **6**) with chemopreventive capacity, extracted from endophytes *Aspergillus fumigatus*, *Fusarium oxysporum, Trametes hirsute, Phialocephala fortinii* as well as some genera belonging to *Trichoderma, Phomopsis Penicillium* [1], and *Alternaria sp* [11]. The chemical tends to adhere to tubulin and limits its action in a reversible manner, causing the karyokinetic spindle structure to be disrupted. Moreover, Podophyllotoxin promotes cell cycle arrest in the G2 phase by eliciting single and double stranded DNA breaks due to their interactions with DNA topoisomerase II [12]. Major derivatives of Podophyllotoxin are Teniposide and Etoposide, which bear diverse therapeutic properties like antiviral, anti-helminthic, antibacterial and chiefly antitumor as mentioned in Fig. (**1**). Additionally, these have been exploited as purgative and cathartic agents in the world of medical science [1, 3, 4, 8, 11, 13].

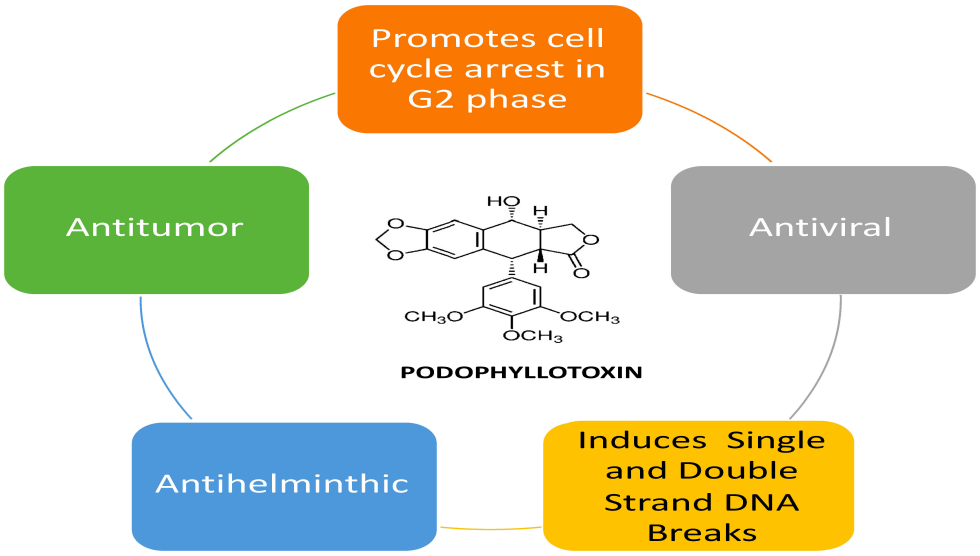

Fig. (1). Major therapeutic properties of Podophyllotoxin.

CHAPTER 12

Immunomodulatory Potential of Bioactives from Selected Ayurvedic Plants

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Abstract: The history of usage of herbal medicine is as old as human civilization. Plant-based drugs have been an invaluable and incredible source for several medical treatments in the traditional system of medicine. With technological advances, it has become possible to get a clear understanding of active compounds behind the therapeutic effectiveness of these drugs. Plant-derived immunomodulators are one such class of compounds, considered safe alternatives than synthetic immunomodulators which cause serious side effects. These agents can increase the body's immune responsiveness against pathogens by activating both the innate and adaptive immune systems. Phyto drugs have gained more interest due to their multi-pharmacological potential of being antioxidant, adaptogen, *etc*. along with immunomodulator. The current book chapter focuses on a few extensively scrutinized immunomodulatory phytocompounds from medicinal plants such as *Tinospora cordifolia, Andrographis paniculata*, Curcuma longa, *Zingiber officinale, Allium sativum, Terminalia chebula,* and *Piper longum*. Phytomedicines from these plants have displayed significant immunomodulatory potential in a variety of experimental (*in vitro* and *in vivo*) models, few compounds have exhibited good therapeutic potential in clinical trials also.

Keywords: Herbal medicine, Immunomodulators, Medicinal plants, Ayurveda, Traditional medicine, Immune system, Phytocompounds.

INTRODUCTION

Human immune system is quite capable to maintain immunity required for protecting the body against diseases or other potentially damaging foreign bodies. Still, certain chemical, biological, physical, physiological factors and adverse en-

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vironmental conditions can alter its normal functioning. In such conditions, immunomodulatory drugs can modify the immune system by either selective inhibition or intensification of immune responsive cells and facilitate the healing in a disease. These drugs can sometimes directly influence a specific immune function or modify components of the immunoregulatory network to achieve an indirect effect on a specific immune function [1].

Discovery of drugs which can selectively stimulate or suppress the immune system paved a new pathway in the management of many diseases where immune dysfunction plays a major role, like autoimmune and infection-associated immunopathologic diseases. Modulators can either be immunostimulatory (developed for their potential applicability to infection, immunodeficiency, and cancer) or immunosuppressive (employed to inhibit the immune response in many immune-mediated diseases *i.e.*, in organ transplantation and autoimmune diseases). Another category is immunoadjuvants, which are usually administered in combination with a main drug to facilitate the immune system by increasing magnitude, duration and induction of antigen specific immune response. Natural, synthetic, recombinant immunomodulatory compounds are widely used as adjuvant/supportive supplementary therapy for prophylaxis and treatment of such clinical conditions. Most of these drugs stimulate the natural and adaptive defence mechanisms enabling the body to heal itself. Monoclonal antibodies, fusion proteins, cytokines and other chemically synthesised compounds are extensively used as immunomodulatory drugs. But major limitations of the use of these agents are their detrimental side effects on general usage. Immunostimulant cytokines like interleukins are also found not fit for prolonged use because of its cost-effectiveness and adverse effects. Therefore, for additional safety and effectiveness, the focus shifted on to herbs and polyherbal preparations which are used traditionally in ethnomedical practices for effective management of wide range of inflammatory and infectious diseases. Exploring the pharmacological action of herbal drugs and its combinations, which bring forth particular therapeutic effect, is an impossible job due to its complex nature. But, from the reverse pharmacological leads, biomolecules isolated from these plants are being widely studied for their immunomodulatory and biological response modifying action. Further research and development are done on these compounds, synthetic modifications are also done at times to optimize the bioavailability and pharmacokinetics [2 - 5]. This chapter presents a review on plant derived biomolecules which have exhibited potent immunomodulatory effects in pre-clinical investigations with wide potential to be used as clinical immunomodulatory agents.

Components of Immune System and Role of Immunomodulators

Immune system is a unique defence arrangement for maintaining homeostasis and providing protection from invading foreign agents by generating interdependent cells. Immune responses are maintained by various organs and cells. Main organs are Bone marrow, Thymus, Spleen and lymph nodes. Bone marrow, the main lymphoid organ, is responsible for production of all blood cells through a process known as Haematopoiesis. From here, the immature thymocytes (prothymocytes) migrate to the thymus and undergo the maturation process (Thymic education) and finally are released in blood stream. These cells with specialized functions work in collaboration to protect the body from infectious microorganisms and also from the growth of tumor cells on account of their capacity to recognize and eliminate the invading pathogens. This capability of resistance against diseases in multi-cellular organisms is described as immunity. Leukocytes developed from bone marrow precursors are the major immune response mediators. Cells like lymphocytes, neutrophils and monocytes/ macrophages, being the fundamental units, act collectively for immune system of the body. The front-line host defence in case of a pathogenic attack is handled by macrophages and mast cells. Macrophages become actively involved in phagocytosis and mast cells recruit eosinophils and basophils to trigger exocytosis. Thymus cells (T cells), bone marrow cells (B cells) and natural killer (NK) cells are the major lymphocytes involved in initiating immune responses. T cells generally differentiate into antigen specific effector cells and B cells into antibody secreting cells. Dendritic cells (DC) are the classical antigen presenting cells with unique ability to capture and present antigens to T cells which are critical for initiating adaptive immune response against infectious agents. Spleen is a blood filter that captures the foreign materials (antigens) mainly by macrophages or dendritic cells and initiates the immune response after presenting the antigen to B and T cells to produce antibodies. Another important organ, lymph nodes, are present throughout the body to act as an immunologic filter for lymph. Here also macrophages or dendritic cells capture the antigen from the site of infection to initiate the immune response. Other than these, there are mucosal-associated lymphoid tissues (MALT), which collect antigens from the epithelial surfaces of the body [6, 7].

Immunity has two components innate and adaptive immunity. In both types of immunity, cells and molecules play a significant role in engulfing bacteria and killing parasites, viruses or tumor cells by secreting activation signals in the form of cytokines, lymphokines or interleukins mediated by T-helper cells. A non-specific (antigen independent) first line barrier for defence against an invading pathogen and injury is innate immunity which leaves no memory. It works efficiently to keep the organism healthy but its deterioration can result in secondary infections leading to serious illness and death. Cytokines, NK cells and

CHAPTER 13

Pharmacological Properties of Bacterial Bioactive Molecules

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Abstract: The pure or standardized extracts obtained from microbes like bacteria, fungi, actinomycetes, *etc*. are considered important sources of bioactive compounds. Some of the microbes show inhibitory action against the growth of certain bacteria, fungi, yeast, insects, *etc*. This provides opportunities for the development of newer drugs and enzymes or beneficial compounds. Large number of bacteria are responsible for producing different bioactive compounds like antibiotics, enzymes, and other secondary metabolites. Some compounds like Gallic acid, Amicoumacin, Prodigiosin, Nystatin, Spinosad, Milbemycin, Lipstatin, Subtilin, Albaflavenone, and Mollemycin A have been studied for their affectivity against bacterial, fungal, insects, pests, *etc*. These compounds are gaining increasing interest because of their unique composition and the possibility of wide industrial applications.

Keywords: Microbes, Bioactive compounds, Bacteria, Pharmaceutical, Drugs, Gallic acid, Amicoumacin, Prodigiosin, Nystatin, Spinosad, Milbemycin, Lipstatin, Subtilin, Albaflavenone, Mollemycin A.

INTRODUCTION

Bacteria play significant role in the production of a variety of bioactive compounds like alkaloids, steroids, terpenoids, peptides, polyketones, flavonoids, quinols and phenols, and natural antibiotics [1]. These compounds enable the interaction of the parent microbe with other microbes and other non-microbial systems. In case of **microbes–microbes interaction,** these compounds are involved in activities like; antimicrobial antibiotics, microbial regulators, growth factors and signaling compounds. In **microbe-lower animals (Invertebrates) interaction** the role of these compounds are as; miticidal, insecticidal, antiparasitic, Anti-feedants (invertebrates), anti-worm *etc*. In the **microbe-higher plants interaction,** the compounds play key roles being plant growth regulators,

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chlorosis inducing factors, and phytoalexins. Lastly in case of **microbe-mammalians** (Humans) interactions, these compounds show activities such as; Antitumor, antibiotics, enzyme inhibition and other pharmacologic activities [2]. Because of their outstanding chemical features, these bioactive compounds have functioned as scaffolds for the development of new products with huge therapeutic and industrial potential. These compounds have greater efficiency and specificity with target sites because of its co-evolution with biological systems [3]. Considering the looming crisis of antibiotic resistance that spreads among plant and bacterial pathogens as well as the increasing incidence of cancer, the hunt for novel, more efficient and less toxic drugs remains a priority. Studies on biochemical properties of natural products derived from microorganisms have elevated incredibly in the last few years because of increasing demand for the compounds having potential pharmaceutical applications or affordable value as cosmetics, drugs, fine chemicals and various personal-care products, potent drugs, and utilitarian home care products [4, 5]. Several bacteria derived compounds can contribute to manage host physiological and pathological states. Metabolomic profiling of gut bacteria can allow to decipher several molecules (among which short chain fatty acids vitamins, and other aromatic compounds controlling cholesterol synthesis, obesity, cardiovascular diseases, metabolic syndrome, *etc*.

The insights acquired within the last twenty years about human microbiota, and its fundamental role in maintaining a healthy physiological status, have opened a new approach to understand the complex reciprocal benefits between bacteria and humans.

Important Bioactive Compounds produced by Bacteria and Cyanobacteria

Gallic Acid

Gallic acid (3, 4, 5-trihydroxybenzoic acid) is produced by *Klebsiella pneumoniae* and *Corynebacterium* sp [6]. Alternatively, gallic acid can be produced by the microbial activity (hydrolysis) of tannic acid by an inducible enzyme tannase (tannin-acyl-hydrolase EC 3.1.1.20 [7].

It acts as a precursor for the commercial production of drug trimethoprim which is an antimicrobial drug. Gallic acid also has extensive variety of biological activities, which includes antibacterial, antiviral, analgesic properties. Gallic acid also contains antioxidant properties which protects human cells against oxidative damage [8]. Beside this gallic acid also performs cytotoxic activity against cancer cells, without damaging normal cells. Due to its therapeutic properties and various commercial applications, it is a compound of notable interest to pharmaceutical industries.

Amicoumacin

Amicoumacin was first recognized in 1980s from marine Gram-positive bacteria *Bacillus pumilus*. Later it was identified in other species of the genus *Bacillus.* It was recently studied that Amicoumacin is responsible for activation of different genes involved in various metabolic pathways. Amicoumacin uses a slightly different way of interaction with mRNA and 16S rRNA molecules. It interacts with mRNA stabilization at the E site rather than displacing it and imply a distinctive way of translation inhibition [9]. Early research of Amicoumacin confirmed that the main mode of action is aimed towards translocation [10].

Prodigiosin

Prodigiosin is a natural pigment produced by marine bacterium *Vibrio ruber,* which has a broad antimicrobial spectrum and is also responsible for inducing autolytic activity in the target cells (i.e., *Bacillus subtilis*). Prodigiosin is a red colored bioactive secondary metabolite produced by both gram-positive as well as gram-negative bacteria. The compound is characterized by pyrrolyl pyrromethene skeleton. Prodigiosins, which are isolated from bacteria and their synthetic derivatives, are identified as effective anti-cancer agents against various cancer cell lines. Prodigiosin contains numerous physiological functions that are associated with antibacterial, antifungal, or antiprotozoal activity [11, 12]. Beneficial effects of various bioactive constituents derived from bacterial source are mentioned in Fig. (**1**).

Geosmin

Geosmin is a bacteria derived odoriferous bioactive compound which imparts the muddy odor with great economic value. This is mainly produced by cyanobacteria. Although, the gene encoding for geosmin is present in other bacteria also like Actinobacteria, Delta and Gamma proteobacteria. The evolutionary history of geosmin gene shows the high sequence similarity of the cyanobacteria geosmin gene with fresh water and soil strains and it is also connected to niche adaptation [13]. Geosmin is highly associated with terrestrial environments. The bacterial species that are responsible for the Geosmin production in soil are actinomycetes – *Nocardia cummidelens; N. fluminea; Streptomyces luridiscabiei; S. albidoflavus* [14]. Geosmin in water bodies affect the migration of anadromous fishes as its presence or concentration in water current guides the glass eels towards the freshwater [15]. Geosmin is responsible for various functions such as predator aversion and also encourages organisms that disperse spores. It also acts as repellant for fruit flies, so that they do not harm the substances on which Streptomyces is growing [16].

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