THERAPEUTIC USE OF PLANT SECONDARY METABOLITES

Editor:

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Therapeutic Use of Plant Secondary Metabolites

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FOREWORD

For centuries, plants have played vital roles in biological beings' economic, social, spiritual, cultural and health wellbeing. Interestingly, through knowledge and advances in research and technology, human beingare gaining a deeper understanding of the significant contributions of plants to human and animal health and development. There is abundant evidence showing that medicinal plants and their secondary metabolites are useful in preventing, ameliorating and in the treatment of various disease conditions such as diabetes, cancer, bacterial, fungal and viral infections. I am aware that many books on medicinal plants and secondary metabolites are in the market and university libraries. However, the current book on "Therapeutic use of plant secondary metabolites" is unique in its content, diversity, and originality of materials. Its depth and expertise of various national and international contributors make it a must-have and a must-read for scientists in the field of medicinal plants, agriculture, food science, postgraduate students, health professionals, and traditional healers. The book covers important topics such as drug discovery and their metabolites in health management, plant secondary metabolites as therapeutic agents in degenerative and microbial infections, etc. The topics are well-structured, covering 15 chapters (chapters 1-15). These topics/chapters provide a framework and stimuli for further in-depth research in the field.

I strongly endorse the book.

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PREFACE

The concept of phytotherapy is as old as mankind. During the last decades, it has become evident that there exist several plants with therapeutic potential, and it is increasingly being accepted that phytotherapy could offer potential lead compounds in the drug discovery/development process. The interest in phytotherapy could be associated with secondary metabolites that could act individually, additively, or in synergy to improve health and wellbeing. Indeed, medicinal plants, unlike conventional drugs, commonly have bioactive constituents working together catalytically and synergistically to produce a combined effect that may surpass the total activity of the individual constituents. The combined actions of these metabolites tend to increase the activity of the main constituent by speeding up or slowing down its metabolism in the body. Also, the secondary metabolites might minimize the rate of undesired adverse effects, and have an additive, potentiating, or antagonistic effect.

The book offers evidence-based mechanistic views on complementary and alternative medicine with a focus on biological mechanisms of action of plant secondary metabolites in degenerative and microbial diseases such as diabetes, cancer, neurodegenerative disorders, antimicrobial resistance, etc., while reporting health benefits. The chapters are written by enviable scholars, lecturers, and experts in indigenous knowledge systems (IKS), industrial and medicinal plants, phytotherapeutics, and phytoinformatics. **Therapeutic Uses of Plant Secondary Metabolites** is timely and highly valuable for both undergraduate and postgraduate students, as well as researchers and professionals in IKS, phytomedicine, ethnopharmacology, phytopharmacology, plant biotechnology, drug discovery and development, and phytotherapeutics.

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CHAPTER 1

The Role of Plant Secondary Metabolites in Health Management

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Abstract: Plant secondary metabolites (PSM) are bioactive compounds produced by plants for protection against predatory organisms and to attract insects for pollination. Recently, greater attention is being focused on PSM due to their perceived ability to elicit pharmacological activities, including antihypertensive, antiarrhythmic, antimalarial, anticancer, analgesic, antispasmodic, antidiabetic, and antimicrobial effects. Therefore, many plant species are continually screened for PSM, such as alkaloids, flavonoids, terpenes, saponins, cardiac glycosides, fatty acids, steroids, and tannins with a view to exploiting them in the manufacture of drugs and pharmaceuticals. In this review, the pharmacological activities and possible mechanisms of action of selected PSM are discussed.

Keywords: Alkaloids, Biological activity, Flavonoids, Polyphenols, Secondary metabolites, Saponins, Terpenes.

1. INTRODUCTION

The term 'metabolites' refers to intermediates and products of metabolism. They are usually small molecules with diverse functions, including structural, signaling, stimulatory, inhibitory, catalytic and defensive roles as well as providing fuel. Metabolites in plants can be of two types namely primary and secondary metabolites. Primary metabolites in plants are essential for life processes such as growth and development of cells. They are produced continuously during growth phase of plants where they are involved in important metabolic processes such as photosynthesis and respiration. Primary metabolites are generally heavy molecular weight compounds with diverse structures, including DNA, proteins, carbohydrates, and lipids.

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Unlike primary metabolites, secondary metabolites refer to a vast and diverse group of active organic compounds produced by plants for the purpose of increasing the likelihood of their survival by repelling or attracting other organisms. This implies that secondary metabolites play a defensive role against herbivory and other interspecies protection. They are not essential for the growth and development of the producing plants and are often differentially distributed among limited taxonomic groups within the plant kingdom. Their absence does not result in plant death but can impair survivability, fecundity, and aesthetics of plants. Apart from the protective role, some secondary metabolites are involved in the pigmentation of flower and seed, which attract pollinators, thereby enhancing seed dispersal and plant reproduction. More importantly, plant secondary metabolites have been reported to possess a myriad of pharmaceutical properties which can be exploited for human health [1]. Secondary metabolites are biosynthesized from primary metabolites by specialized cell types at distinct developmental stages. They are generally low molecular weight compounds, varying in quality and quantity for a specific plant species depending on location.

The main biotic factor that affects plants is a pathogenic infection caused by bacteria, viruses, fungi, and nematodes. Other biotic antagonists include attacks by mites, insects, mammals, and other herbivorous animals and competition from other plants arising from parasitism and allelopathy. The most significant abiotic environmental stresses faced by plants are excessive temperature and water as well as exposure to radiation and chemicals. To combat these stress factors, plants have evolved a defensive system involving the production of secondary metabolites, which serve to protect against predators and microbial pathogens [2]. These natural products are able to perform a defensive role due to their toxic nature, which allows them to repel herbivores and microbes as well as dominate other plants within the same locality [3]. One of the mechanisms employed by secondary metabolites is acting as antimicrobial agents, which may be pre-formed or induced by infection. Other modes of defense include formation of polymeric barriers to prevent penetration of pathogens, and synthesis of enzymes capable of degrading pathogenic cell wall. It is also possible for plants to employ secondary metabolites as specific recognition and signaling systems, which allows rapid detection of pathogenic invasion and triggering of defensive responses.

Plants can also efficiently respond to environmental stresses through sensors regulated by feedback mechanisms. To achieve this, plants use secondary metabolites as messengers under sub-optimal conditions to trigger their defense mechanism, which involves the production of phytochemicals, hormones and a variety of proteins necessary to protect the ultra-structure of plants from such hazards [4]. Elevated synthesis of secondary metabolites has also been observed under abiotic stresses like salinity and drought. These are utilized efficiently in defense mechanisms and biochemical pathways facilitating water and nutrient acquisition, chloroplast function, ion uptake and balance, synthesis of osmotically active metabolites and specific proteins, production of metabolites acting as osmo-protectants and detoxifying radicals [5].

2. CLASSIFICATION OF PLANT SECONDARY METABOLITES

It has been estimated that well over 300,000 secondary metabolites exist in nature [6]. There is no rigid scheme for classifying these secondary metabolites due to their immense diversity with respect to structure, function, and biosynthesis. Hence, it is difficult for them to fit perfectly into a few simple categories. For ease of reference, PSM may be grouped based on the presence of a recurring structural feature. For example, flavonoid compounds are oxygenated derivatives of aromatic ring structure, while alkaloids having an indole ring are called indole alkaloids. Terpenes consist of five carbon isoprene units, which are assembled in different ways.

PSM may also be classified according to the genus to which the plant source belongs. For example, morphine and codeine are examples of opium alkaloids. Grouping is also possible according to biological activities and physiological effects they elicit, such as antimicrobials, antibiotics, analgesics, *etc*. PSM can also be classified based on similarities in biosynthetic pathways. Generally, classifications based on structure and biosynthesis are more realistic and make the most sense.

3. POLYPHENOLS – A MAJOR CLASS OF PLANT SECONDARY METABOLITES

Polyphenols are secondary metabolites essential for the protection and survival of plants. They represent one of the most widespread groups of secondary metabolites in plants, with more than 8,000 identified phenolic structures [7]. These compounds can be found in almost all organs of plants, where they perform a myriad of functions, including skeletal constituents of different tissues and pigmentation of several plant organs [8], defense against various pathogens [9] and signaling molecules in plant cells [10]. The main sources of phenolic compounds are woody vascular plants, especially bark.

3.1. Classes of Polyphenols

Fig. (**1**) depicts the sub-divisions of polyphenols into different classes based on their chemical structures, namely phenolic acids, flavonoids, stilbenes and lignans [11, 12].

CHAPTER 2

Medicinal Plants and Drug Discovery

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Abstract: Emerging communicable diseases, such as Ebola and Coronavirus Infection Disease (COVID-19), and non-communicable diseases related to diet and lifestyle, *e.g.*, diabetes, have been increasing over the last two decades, having a great negative impact on the health services, which are already over-stretched. This again has been compounded by some largely unresolved diseases, such as malaria and HIV/AIDS, which are common parasitic and infectious diseases in many developing countries. Over several years, natural medicine has been a dependable alternative in the prevention and treatment of diseases and has been widely recognized as important for drug discovery and development. Over the world, traditional medicine has largely depended on natural products. The structural diversity and biological activity of natural products have made them a valuable source of drugs and drug leads. Several active compounds have been isolated from natural products. Among them, some follow their traditional uses while some others do not. For many years, plant's bioactive compounds, otherwise referred to as secondary metabolites, have been the source of countless compounds and leads for drug discovery. The process of drug discovery includes the identification of a lead compound, which is then proposed for drug development. Drug discovery, therefore, encompasses moving from a screening hit to a compound becoming a therapeutic agent. It is a process that requires expertise and experience. In modern drug discovery research, techniques commonly employed include combinatorial chemistry, high-throughput screening, bioinformatics, proteomics and genomics.

Keywords: Drug development, Drug discovery, Drug leads, Natural products, Plant.

1. INTRODUCTION

As the world faces global health challenges, the importance of research into drug development through natural products has become increasingly important. Plants, animals and minerals are among the natural products that have been the basis for the treatment of many diseases for centuries [1].

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Recently, much attention has been paid to pharmacognostic, phytochemical and pharmacological studies of traditional medicinal plants.

Medicinal plants are of vital value to the pharmacological systems since they possess multiple compounds, especially the lead molecules and thus have a number of advantages compared to synthetic molecules [2, 3]. Among natural products, plant metabolites have been revered for their usefulness as either drugs or drug precursors, being described as biosynthetic laboratories where chemical compounds could be extracted to serve multiple physiological functions [4]. Ethnopharmacological knowledge has offered a boost to the discovery and development of active and medicinally important compounds from plants. The approach is based on a body of work across several disciplines, including botany, chemistry, and pharmacology. Ethnopharmacology encompasses field observations, descriptions of the utilization and bioactivities of folk remedies, botanical identification of the plant material as well as phytochemical and pharmacological research. The study provides opportunity to explore the vast opportunities, chemical uniqueness and diversities that are present in the natural products, either as purified compounds or as crude extracts of the plant [2, 5]. The understanding of green pharmaceuticals is becoming increasingly popular and highly important as the world searches for new drugs [2]. The medicinal value of plants has come to recognition since ancient times, and available records have shown the use of many plants derived medicines for managing pathological conditions since time immemorial [6 - 8]. Literature search has shown that while some of these medicines have been used as concoctions, others have been used as crude plant extracts without the isolation of target active compounds that elicit the therapeutic function [8].

The isolation and application of bioactive plants' constituents in modern drug discovery started in the 19^{th} century, and as of today, several active compounds with definite chemical structures have been identified in plants and are used globally as drugs [9, 10]. Compounds isolated from plants have shown some remarkable efficacy against some of the world's most challenging diseases and clinical conditions, including multi-drug resistance [11], cancer [12, 13], depressive disorders [14], diabetes [15], pest invasion [16], inflammation [17], and viral and other parasitic infections [18, 19]. The engagement of enthnobotanical and ethnopharmacological knowledge in the hunt for new medicines has offered a new route to further explore the different compounds in plants which could be important as a new class of drugs.

Despite the fact that ethnobotanical discoveries are essential factors for the development of modern medicine, globalization and urbanization have led to the disappearance of traditional medicinal plant knowledge [3, 20]. The adoption of plants in the making of edible vaccines poses a very interesting breakthrough with respect to the constraints of traditional vaccines [21]. Edible vaccine has the potential for global immunization against diseases that have been known to be pathogenic and their concrete exploration could bring a new evolution and approach to public health and medicine [21]. The decisive role played in pharmaceutics by plants since the prehistoric times could be further enhanced through the knowledge of phytomedicine and nanophytomedicine, and drugs could be developed from plant chemicals for specific targets in the system [22].

2. HISTORICAL USE OF PLANTS FOR PHARMACOLOGICAL PURPOSES

Life basically depends on plants as they occupy the central position in the ecosystem. The mankind has discovered the numerous benefits of the plant kingdom and has gainfully explored them not only as a source of food needed to survive but also as medicine [23]. How did man discover the therapeutic benefits of plants? Trial and errors may have acquainted man with the preparation of medicine and food from plants, and through this, he has mastered the act, built on the accumulation of experiences, and thus, is in a better position to harness the resources in his environment to meet his life needs [7, 23]. The experiences and information gathered have outlived every generation through information transmission. The evolution of the technologically driven generation, which gives prompt access to modern facilities, has brought an abundance of knowledge to human about natural resources and the use of the plant for multiple purposes [7]. Report from literature indicates that the use of plants for the treatment and prevention of diseases has its origin in the ancient Chinese, Egyptians, Indians, Greeks, Romans and the old Slavs, from where it spread across other nations of the world [23].

Traditional medicine generally describes knowledge about health, skills and practices that are peculiar to different cultures around the world, and this informs why early practices showed that there was diversity in drug development concepts [24]. Reports indicate that before the advent of the 20th century, man depended essentially on the use of crude and unpurified plants, animals and microbes' extracts for treating diseases. In the early 20th century, researchers were able to show that for medicinal activity, specific interactions occur between drug molecules and the living system [23]. This interaction is mediated by receptors which are cellular macromolecules, *i.e.*, proteins and nucleic acids. Thus, scientists have concluded that plant extracts contain chemical constituents generally referred to as bioactive compounds that elicit biological effects through interactions at target sites. In 1805, morphine, the first bioactive pharmacological compound, was isolated from opium by a German apothecary assistant Friedrich

CHAPTER 3

Therapeutic Properties of Bioactive Secondary Metabolites in Essential Oil Crops

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Abstract: Medicinal herbs and their essential oils (EOs) are of commercial and industrial importance with diverse uses as forage and fiber crops, in food, cosmetics, perfumery and chemical industries, and in traditional medicine due to their phytochemical constituents and bioactivities. This chapter was aimed at documenting the therapeutic properties of major secondary metabolites in EOs extracted from six selected economically important medicinal herbs (*Achillea millefolium* L., *Melissa officinalis* L., *Origanum majorana* L., *Pelargonium graveolens* L'Hér. *Rosmarinus officinalis* L. and *Thymus vulgaris* L.). Forty-five compounds (mainly monoterpenes) were recorded as major compounds of the six medicinal herbs. The compounds possess varying biological activities, which include antimicrobial, anti-inflammatory, antioxidant and cytotoxicity properties. Other activities reported were antinociceptive, neuroprotective effects, acetylcholinesterase inhibition, anti-ulcerogenic, DNA protection, glutathione S-transferase activity, chemoprotective, anti-depressant and sedative effects. The compounds showed potential to be used as alternative agents as drugs, cosmetic ingredients and food additives. Though some scientific evidence has confirmed the use of these herbs in various industries, much work still needs to be done to comprehend the therapeutic application of their EOs and phytoconstituents to benefit from their full potential.

Keywords: Antimicrobial, Antioxidant, Cytotoxicity, Medicinal herbs, Phytochemicals.

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1. INTRODUCTION

Plants are sources of secondary metabolites with curative properties. These secondary metabolites are distributed within limited taxonomic groups and are produced by plants in their interaction with the environment for adaptation and defense [1]. They are generally responsible for specific odours, tastes, and colours in plants [2], and are sources of food additives, flavors and industrially important pharmaceuticals [3]. Most of these compounds have imperative adaptive protection against herbivores, pests and microbial infections, while some serve as attractants for pollinators and seed-dispersing animals, and as allelopathic agents [4, 5]. On the other hand, primary metabolites (such as acyl lipids, nucleotides, amino acids, and organic acids) are produced by all plants and are essential for basic life functions such as cell division and growth, respiration, and reproduction [1, 6]. Secondary metabolites are classified according to their biosynthesis pathway into phenolics and phenylpropanoids, terpenes and steroids, and alkaloids [7]. The most common pathways for the production of secondary metabolites include pentose (glycosides); shikimic acid (phenols, tannins, aromatic alkaloids); acetate – malonate (phenols, alkaloids) and mevalonic acid (terpenes, steroids, alkaloids) [8].

For centuries, secondary metabolites have been used in traditional medicine for their therapeutic properties to relieve human ailments, including chronic diseases [6]. The production of secondary metabolites in plants is greatly influenced by environmental factors such as temperature, humidity, light intensity, moisture, and mineral nutrient availability [9] as well as biotic factors. Naturally, their production is very low and dependent on the physiological and development stage of the plant [10]. Currently, there are numerous biotechnology strategies (*e.g*. plant cell, tissue and organ cultures) that have been developed to increase the production of secondary metabolites *in vitro* to meet their commercial demand [6, 10]. Secondary metabolites demonstrate numerous biological activities that stimulate their use in pharmaceutical, cosmetics, aromatherapy and nutraceutical industries. The secondary metabolites in plant extracts and essential oils (EOs) are responsible for diverse biological properties [11], such as antidepressant [12], antimicrobial [13 - 18], anti-inflammatory [19], antimutagenic [20], chemoprotectant [21, 22], antioxidant [16, 23], DNA damage protection [23] and antiviral activities [24, 25].

This chapter was aimed at providing an appraisal of the therapeutic properties of major secondary metabolites in EOs extracted from six selected economically important medicinal herbs (*Achillea millefolium* L., *Melissa officinalis* L., *Origanum majorana* L., *Pelargonium graveolens* L'Hér., *Rosmarinus officinalis*

L. and *Thymus vulgaris* L.) as a case study. The majority of the selected herbs belong to the Lamiaceae family and are of great economic and industrial importance. They are widely used in the food industry for food flavoring or as seasoning agents and are popular as perfume ingredients in cosmetics and household cleaning products [26]. In addition, they are used in traditional medicine to treat many ailments, including asthma, indigestion, headache, rheumatism [22], as tonic, antispasmodic, carminative, diaphoretic, surgical dressing for wounds, sedative-hypnotic strengthening the memory, relief of stress-induced headache [27], against colds, and in functional disorders of the circulation [28].

2. SECONDARY METABOLITES AND THEIR ROLE IN PLANTS

Secondary metabolites in plants are the active components responsible for their therapeutic properties [29]. These compounds are produced for diverse purposes, such as protection against biotic and abiotic factors [30], to counteract or in response to environmental stimuli, and to tolerate certain stress conditions [31]. Abiotic stress triggers the generation of reactive oxygen species (ROS), which alter plant metabolic processes. Consequently, excessive ROS in plants can damage plant cells through the oxidation of biological components such as nucleic acids, proteins, and lipids [32]. Although plants possess antioxidant defense capacity and repair mechanisms, oxidative damage results from the imbalance between this capacity and the rate of ROS accumulation [33].

Plants develop antioxidant defense system and produce compounds such as brassinosteroids to scavenge the excessive accumulation of harmful ROS [32]. The intrinsic antioxidant defense system consists of many enzymatic, non-enzymatic, lipophilic and hydrophilic molecules, which allow for the adaptation of plants to different environments, maintain homeostasis and detoxify ROS. The secondary metabolites sustain plants through their stress regulatory and growth-promoting activity by directly quenching or removing ROS, or by indirectly influencing hormone-mediated signaling to up-regulate defense genes. Even though there will always be a standard level of secondary metabolites in a plant produced during biosynthesis, some plant parts may contain higher concentrations of secondary metabolites at different stages of plant growth.

Secondary metabolites serve as defense compounds against bacteria, fungi, viruses, herbivores and other competing plants [34]. Additionally, some plants can use secondary metabolites for communicating with other plants by sending signals, and between plants and symbiotic microorganisms [35]. They also serve as an attractant to pollinators and seed dispersal animals; and for these reasons, they have been explored for biopharmaceutical purposes [36]. Many secondary

CHAPTER 4

Bioactive Compounds as Therapeutic Intervention in Cancer Therapy

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Abstract: Neither transmittable nor communicable, painstakingly the second most fatal disease worldwide, cancer has gained the interest of scientists who are attempting with tenacity to decrypt its unknown facets, discover new diagnosis techniques, as well as to create improved and more efficient treatment methods. A major impediment to effective cancer therapy is the inability to destroy the complete malignant tumour growth and evolution of tumour resistance. Chemotherapeutic drugs are known for their cell death mode of action, thereby incapacitating non-cancerous cells in the process. A successful anti-cancer drug should kill or debilitate cancer cells without causing unnecessary damage to normal cells. Administration of natural bioactive compounds exemplifies an alternative technique as they are associated with lower toxicities. These bioactive molecules are effective and demonstrate great specificity as they possibly operate as potent anti-oxidants and apoptosis inducers. Moderating apoptosis might be helpful in managing, treating, or deterring cancer. Significantly, bioactive compounds are providing such templates. Plants have a long history in cancer treatment. More than 3000 species have been known for their anti-cancer potential. Over 60% of currently used anti-cancer agents are derived in one way or another from higher plants. This chapter describes the roles and advancements of the use of bioactive compounds in the treatment of cancer.

1. INTRODUCTION

Cancer is ranked as the second most cause of death globally. A major challenge for effective treatment of cancer is the absence of obliteration of the entire tumour cell population and the subsequent development of chemoresistance. In the past 50 years, considerable progress has been made in recognizing the molecular basis of cancer. Some anti-cancer regimens do exist, although they are linked with excessive toxicity. During the 1960s, the National Cancer Institute (USA) started to screen plant extracts with antitumor activity [1].

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Bioactive compounds isolated from medicinal plants, as powerful foundations of new anti-cancer drugs, were found to be of growing interest from then on. Administration of these bioactive compounds in low concentrations can be fatal for microorganisms and small animals however, in larger organisms, including humans, they might explicitly alter the fastest-growing tissues like the tumours [2].

We stand at a turning point in cancer therapy. The last 60 years have been dominated by drugs, which are not limited to cancer cells. Being non-specific, these drugs also destroy normal cells and can cause serious and often deadly adverse outcomes during the process. However, the future does look promising for possible success in the struggle against cancer. As a science, the use of bioactive compounds from plants acts as an anti-oxidant and can contribute to inducing signalling pathways, including apoptosis. From many natural compounds investigated, several have been shown to be promising based on their anti-cancer effects related to apoptosis. This ultimately may lead to a greater impact on tumours specifically, thus leading to the development of successful treatment.

2. CANCER AND APOPTOSIS

2.1. Global Prevalence of Cancer

Cancer is a massive hurdle in improving the average lifespan in all countries of the globe in the 21st century. In the year 2018, an estimated 9.6 million deaths occurred due to cancer [3]. On a global scale, the collective probability of prevalence indicates that 1 in 8 men and 1 in 10 women are going to develop the illness during their lifespan. By 2050, the global burden is expected to grow to 27 million new cancer cases and 17.5 million cancer deaths [4].

Cancer morbidity and mortality rates are increasing precipitously. The common rationalizations are aging and expansion of the populace, as well as socio-economic development [5]. Environmental factors, such as tobacco use, urban development, and its associated pollution, as well as changing diet patterns, also contribute immensely to the cause of this disease. The most diagnosed cancers worldwide are lung, breast, and colorectal cancers (Fig. **1**). The most common causes of cancer-causing deaths are lung, stomach, and liver cancers.

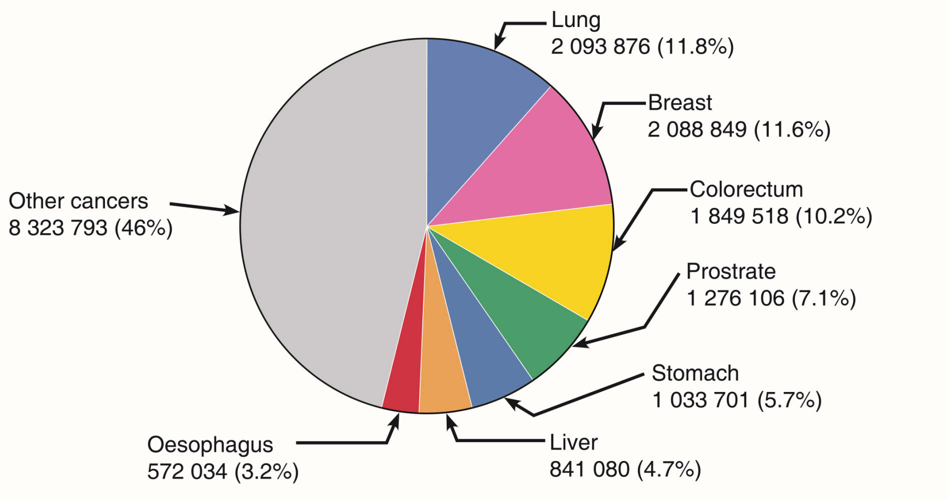

Fig. (1). The distribution of all-cancer types as well as incidence and mortality globally, for both sexes combined [3].

2.2. General Features of Cancer

Cancer is a disease in which abnormal cells divide without being regulated and can invade other tissues. This is not just one disease but many diseases. Cancer cells may spread to other components of the body through the bloodstream and lymph systems. There are more than 100 different types of cancer. Most cancers are named for the organ or type of cell in which they start.

Cancer occurs when a cell obtains adequate mutations to allow it to survive and multiply free from its normal regulation by soluble extracellular factors and by interaction with its neighbours. The genes that become deregulated are the key proteins that manage these processes. These proteins can be placed into three overlapping categories: (i) those that control signal transduction of extracellular signals regulating cell division; (ii) those that control processes associated with cell invasion; and (iii) those that affect processes associated with the cell cycle and apoptosis. In some cases, the proteins that control these processes become mutated, and they function inappropriately [2].

2.3. Pathophysiology of the Carcinogenic Process

The loss of self-controlled expansion is the enduring effect of the build-up of anomalies in various regulatory systems. This, therefore, results in alterations of cell mechanisms that differentiate cancerous cells from normal healthy cells [6]. The carcinogenic process that arises by the accumulation of mutations in these

CHAPTER 5

Bioactive Compounds as Therapeutic Intervention in Mucocutaneous Cancers

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Abstract: There are several beneficial effects of plant bioactive compounds in the evidence-based prevention and treatment of mucocutaneous cancers. For instance, several bioactive compounds *via* various antioxidant and immunomodulatory mechanisms have been shown to positively improve different diseases, including cancer. Considering the complex, multifactorial processes that regulate genetic and cellular function in cancer development, the use of small phytochemical molecules capable of targeting multiple carcinogenetic genes and pathways is plausible.

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Furthermore, the identification of molecular targets and cognate dietary bioactive molecules in mucocutaneous cancer, using applied combinatorial chemistry approaches, potentially presents a key complementary ancillary tool for developing robust, physiologically bioavailable, diversity-oriented, and cost-effective therapies. These systems biology and omics-based theragnostic tools are crucial for the management of cancers that affect the oral mucous membranes and skin in a resource-limited setting. Natural products and nutraceuticals are poised to ameliorate the burden of mucocutaneous cancers and improve the drug discovery pipelines if state-of-the-art research techniques are used to elucidate their therapeutic values in the era of precision medicine. Hence, this review focuses on the currently available and potential therapeutic benefits of plant bioactive compounds in the prevention and management of mucocutaneous cancers.

Keywords: Bioactive compounds, Mucocutaneous cancers, Oral cancer, Phytocompounds, Skin cancer, Therapy.

1. INTRODUCTION TO MUCOSAL AND SKIN CANCERS

The human surface covering (skin) adapts to the physiological demand of its local environment to either form mucosa or skin [1]. Furthermore, there are different physiological, anatomical and histological modifications of skin (*e.g.*, acral, non-acral) depending on the requisite function of the skin [2]. Even within the oral mucosa, there are functional transitions and keratinization changes [1, 3] from mucosa to the gingiva, at the muco-gingival junction [4 - 6]. The junction where skin transitions to form mucosa is known as mucocutaneous junctions [7 - 9], and has been shown to be a source of mitotically active transient amplifying cells [7]. In addition, reticular and papillary micro-vascularization networks with extensive capillary looping with the deep reticular networks have been identified as characteristic of the mucocutaneous junctions of the eyelids and lips [9]. The anatomical contiguity of skin and mucosa structures, and the spatio-physiological adaptation of the skin and mucosa structures, demand a holistic approach to a systematic understanding of its pathologies and effective personalized and targeted therapies.

A report has shown that melanoma skin cancers affect about 132,000 people globally, and non-melanoma skin cancer has an estimated incidence of *ca.* 2-3 million people every year worldwide [10]. Skin cancers are typically divided into two major groups: melanoma and non-melanoma skin cancer (NMSC). The most common NMSCs are SCC and basal BCC [11]. Other NMSCs include cutaneous lymphoma, Merkel cell carcinoma, and Kaposi's sarcoma [11]. Using available literature evidence, we discuss in this chapter the role of bioactive compounds in three common mucocutaneous cancers, *viz*: malignant melanomas (MM), basal cell carcinomas (BCC) and squamous cell carcinomas (SCC).

1.1. Melanomas

Melanoma is a malignant melanocytic neoplasm that occurs as a result of accumulated genetic dysregulation [12]. Melanomas arise from dendritic melanocytes, which are neuroectodermal-derived cells situated in the basal layers of the skin, skin, eye, mucosal epithelial and meninges [13, 14]. Melanomas can develop from both cutaneous and mucosal surfaces [15]. Frequent melanoma sites include the head, neck, and lower extremities. Less frequent sites are oral and genital mucosa, nail beds, conjunctiva, oesophagus, nasal mucosa, vagina and leptomeninges [13].

Mucosal melanomas are tumours that arise from the melanocytes situated in the epithelia of the nasal cavity, oropharynx, gastrointestinal tract, and genitourinary tract [16]. Mucosal melanomas are uncommon and account for approximately 1.3% of all melanomas [17]. Approximately 50% of mucosal melanomas affect the head and neck region accounting for about 9% of all malignant head and neck tumours [14]. Mucosal melanomas are more aggressive than cutaneous melanomas, and approximately one-third of patients with mucosal melanoma present with advanced disease [16, 17]. Cutaneous melanoma is linked to exposure to ultraviolet light, but the anatomic location of mucosal melanoma excludes ultraviolet light exposure as a risk factor [17]. The overall 5-year survival rate is 25% despite the aggressive surgical intervention and adjuvant treatment therapies [16]. The aggressiveness of mucosal melanoma may be clarified by its late presentation and late diagnosis, vascularity of the mucous membranes, which promotes hematogenous metastases [16].

1.2. Basal Cell Carcinoma

Basal cell carcinoma (BCC) is a non-melanoma skin cancer. Approximately 80% of non-melanoma skin cancers are BCC [18], making it the most common skin cancer type globally [19]. BCCs arise from basal keratinocytes of the epidermis, hair follicles and eccrine sweat ducts [18]. BCCs are basophilic with large nuclei, and they require surrounding stroma for support during growth [18]. BCCs are usually slow-growing, and they rarely metastasise; however, delayed or inadequate treatment may lead to significant morbidity arising from destroyed skin, tissue, cartilage and bone [20]. There are five main histologic patterns of BCC: nodular, micronodular, superficial, infiltrative and morpheaform [18]. Risk factors for the development of BCC include ultraviolet radiation, immunosuppression, genetic disorders and age [19]. Most patients affected by BCC are middle-aged or the elderly [20]. Approaches for treating BCC can be surgical or non-surgical. Surgical techniques include curettage and cautery, cryosurgery, excision and Mohs micrographic surgery [20].

CHAPTER 6

Bioactive Compounds as Therapeutic Intervention in Bacterial Infections

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Abstract: This study highlights the significance of drug resistance towards difficulties in the treatment of infectious diseases, the essence of bioactive compounds in therapeutic intervention, and the unique approach employed by bioactive compounds away from conventional synthetic drugs. Literature was gathered from different online databases to retrieve the required information. Bacterial resistance to antibiotics is a major concern that threatens clinical efforts in treating bacterial infections. This has grossly reduced clinical success on previously curable infections and/or sometimes results in a prolonged hospital stay. Antibiotics provide protection and remedy against infectious diseases. But the emergence of multi-drug resistance strains has inflicted untold loss of effectiveness on virtually every conventional antibiotic. Hence, scientific communities are propelled into seeking alternative therapies in a bid to mitigate the overwhelming consequence on public health. Bioactive molecules are important sources of newly derived therapeutic agents. They have minimal likelihood of inducing unintended immune reactions, reduced level of toxicity; are structurally diverse in nature, exhibit broad-spectrum therapeutic effects. Bioactive molecules are commonly present in small amounts in plant-based foods; and provide health benefits in addition to the basic nutritional values expected in foods. Several plant-based bioactive principles serve as inhibitors for drug resistance in order to enhance the effective delivery of the antibacterial compounds. Meat products are a good source of non-plant bioactive molecules, which are expressed in the form of peptides, vitamins, minerals and fatty acids. Other important sources include endophytic bacteria, endophytic fungi, probiotic bacteria, actinomycetes and marine organisms. Natural products are relatively

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safe when compared to their synthetic counterparts. As newly manufactured potent antibiotics become increasingly unavailable and/or unaffordable, bioactive compounds present viable alternatives. They are readily available and are derived from inexpensive raw materials *via* cheap technology.

Keywords: Alkaloids, Antimicrobials, Bacteriocins, Natural products, Phenols, Super burgs.

1. INTRODUCTION

The resurgence of multi-drug resistant bacterial pathogens of infectious diseases has significantly reduced therapeutic options in the clinics, hence propelling the scientific communities into seeking alternative therapy in a bid to mitigate the overwhelming consequence on public health. The resurgence has led to reduced clinical success on previously curable infections and in some cases, results in a prolonged stay in hospitals [1, 2]. Antibiotics, as natural or synthetic organic molecules, are lethal to microorganisms; and provide protections and remedies against infections caused by bacteria pathogens. However, the emergence of multi-drug resistance strains has inflicted untold loss of effectiveness on virtually every conventional, including the frontline, antibiotics [3].

Bioactive compounds are secondary metabolites produced by some living cells and are capable of therapeutic potentials; exhibit prophylactic and immunomodulatory activities; mitigate toxin effects; reduce oxidative stress; and enhance effective metabolism [4, 5]. Bioactive molecules are commonly present, in small amounts, in plant-based foods and provide health benefits in addition to the basic nutritional values expected in foods; hence, they are said to be non-nutrient food components that exhibit medicinal effects in living systems when ingested [6]. The presence of these molecules has been speculated to be responsible for the evidenced-based potential health benefits attributed to the adequate consumption of fruits and vegetables [7].

Moreover, there has been increasing interest in the medicinal advantages of these bioactive molecules. Plant-based foods and traditional medicinal plants employed in folklore remedies have been the primary source of these active molecules [5, 8]. Though in recent times, more considerations have equally been given to the non-plant entities, such as microorganisms and meat products, as other rich sources of bioactive agents of therapeutic importance [9]. The increasing awareness of the valuable medicinal features of the bioactive compounds has warranted the need for a collective effort among stakeholders to provide an accessible database containing required basic information on these compounds. The available public database in this respect includes USDA flavonoid content of selected foods [10]; Phenol-Explorer: database for polyphenols in foods [11]; and EuroFIR eBASIS: Bioactive Substances in Food Information Systems [12].

Natural products have been the most important source of bioactive molecules while plants and microbes have been the centre of this for valuable drug discovery [13, 14]. Bioactive compounds are made up of extremely heterogeneous classes of compounds with structurally diverse chemical compositions and are widely distributed in nature. They have a different range of concentrations in both plants and animals; they also have specific sites of action for their biological activities and are equally effective against reactive oxygen species [15]. Meat products are a good source of non-plant bioactive molecules where they are expressed in the form of proteins/peptides, vitamins, minerals and fatty acids [16]. Other important sources include, endophytic bacterial [17], endophytic fungi [18], probiotic bacteria [2], actinomycetes [19] and marine organisms [20] (Fig. **1**). Several organisms in the oceanic ecosystems are indispensable sources of natural products endowed with ranges of structural diversities and significant bioactivities for human applications [21]. The marine environment is highly rich in biological and chemical diversity. Due to the extremity, aggressiveness and competitiveness associated with the marine environment, organisms therein produce several secondary metabolites with promising potential therapeutic agents, nutritional supplements and agrochemicals [20].

Polyphenols are among the most prevalent and diverse groups of secondary metabolites, produced by plants and other organisms and are noted for their potential against quorum sensing, detoxification and formation of biofilm by pathogens [22]. Alkaloids, on the other hand, provide the underlying structures for the development of a great variety of antibiotics with a wider range of actions [23]. The bacteriocidal effect of tannins against pathogens is not limited to plasma membrane destabilization; it also involves inhibition of extracellular enzymes, disruption of metabolic pathways and blockage of the trace-nutrients required for cell growth [24]. Terpenoids are another abundant group of valuable natural products that play important roles in plant defence against pathogens and pest attacks and are widely used in pharmaceuticals for drug discoveries [25]. Moreover, saponins, due to their amphipathic property, have also been a valuable natural product employed in the development of drugs, cosmetics, and surface disinfectants against bacterial contamination, while several studies have also reported their activities against bacterial pathogens [26, 27]. The ability of some of these metabolites, and several others in their category, to modify resistance features in a pathogen provides a hedge in the combat against the spread of bacterial resistance [23].

CHAPTER 7

The Use of Plant Secondary Metabolites in the Treatment of Bacterial Diseases

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Abstract: Plants produce an array of secondary metabolites identified as possible anti-microbial agents that are used across the globe to treat numerous diseases and ailments. These secondary metabolites serve as unique commercial sources of various pharmaceuticals, food additives and flavouring agents, and possess diverse industrial applications. Alkaloids, flavonoids, and polyphenols are secondary metabolites shown to attack numerous gram-positive and gram negative bacteria in response to microbial infections. Secondary plant metabolites have a detrimental effect on microbial cells in several ways, such as alteration of the structure and function of the cytoplasmic membrane as well as DNA/RNA synthesis, interference with intermediary metabolism, interaction with membrane proteins, a disruption in the movement of protons leading to ion leakage, enzyme synthesis inhibition, the clotting of cytoplasmic components and interference in typical cell communication. This ultimately results in cell death. The focus of this chapter is to provide an overview of the function and benefits of plant secondary metabolites as therapeutic agents to combat pathogenic bacterial infections.

Keywords: Alkaloids, Anti-microbial agents, Bacteria, Infectious diseases, Medicinal plants, Secondary metabolites.

1. INTRODUCTION

Mankind has used several plants and their derivatives for medicinal purposes, since ancient times, especially for the treatment of infectious diseases. An excellent example of this is quinine, an alkaloid derived from the cinchona tree bark. Achan *et al*. [1] has reported on this alkaloid as a treatment for malaria and infectious diseases such as pneumonia and typhoid fever. Another wondrous anti-

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microbial agent is cinnamon which is widely used in ancient Chinese medicine and has multipurpose applications due to its main biologically active agent, cinnamaldehyde [2]. There are several remedies that stem from traditional therapeutic practices which require the biological activity of various substances derived from plants to treat different diseases, including bacterial infections. Several of these traditional remedial practices are still extensively used currently. Several drugs that are currently used in medicine come from folk medicine [3].

Secondary plant metabolites, a group of biochemical substances produced by metabolic pathways of plant cells, have shown to promote the curative effects of plants. Contrary to primary metabolites, namely nucleic acids, amino acids, carbohydrates, and fats that are essential for survival, secondary metabolites are not crucial for plant growth but play a vital role in the competition between species and provide a defense against insects, herbivores, and microbes [4 - 11]. Kessler and Kalske [12] have reported that "approximately two-hundred thousand different secondary metabolites have been isolated and identified," which were grouped in accordance with the chemical structures and/or biosynthetic pathways [13].

These secondary metabolites have been simply classified into four main groups based on their chemical structures (Table **1**): terpenes (polymeric isoprene derivatives), phenolics (comprising of one or more hydroxylated aromatic ring), sulphur-containing compounds (lectins, defensins, phytoalexins and thionins) and compounds containing nitrogen (amino acids and alkaloids that lacks protein). In combination, these groups make up about 90% of all secondary metabolites [14, 15]. There are minority groups which are inclusive of saponins, lipids, essential oils, carbohydrates, and ketones [16]. Secondary metabolites are extensively used in many pharmaceutical and food industries in the production of perfumes, agrochemicals and cosmetics [3, 17]. The use of these secondary metabolites as anti-microbial agents targeting a number of pathogenic microbes is endless. Phytochemical screening of various plants has revealed several bioactive compounds such as alkaloids, flavonoids, terpenes, tannins, quinones and resins that possess antibacterial properties [18]. These could be used exclusively or as a combination to enhance the mechanism of action of conventional antibiotics. This is relevant due to the rapid emergence and dissemination of drug-resistant microorganisms [19, 20]. With the wide diversity of substances that are produced by a variety of plants, many have been discovered and studied. However, there are several that are yet to be discovered and some that are still not sufficiently studied. The antibacterial activities of many plants have been extensively researched, such as the crude extracts of basil, garlic, cinnamon, ginger, mustard and other herbs that exhibit anti-microbial properties against numerous gram-positive and gram-negative bacteria [21].

Table 1. Types of secondary metabolites of plants (adapted from Ramirez-Gomez *et al.* [22]).

Classification	Types	Example
Terpenes	Monoterpene	Geraniol
	Sesquiterpenes	Humulene
	Diterpenes	Cafestol
	Sesterpenes	Geranylfarsol
	Triterpenes	Squalene
	Sesquarterpenes	Ferrugicadiol
	Tetraterpenes	Lycopenes
	Polyterpenes	Gutta-percha
Phenolics	Coumarin	Hydroxycoumarins
	Furano-coumarins	Psoralin
	Lignin	Resveratrol
	Flavonoids	Quercitin
	Isoflavonoids	Genistein
	Tanins	Tanins acid
N containing compounds	Alkaloids	Cocaine
	Cyanogenic glucosides	Dhurrin
	Non-protein amino acids	Canavanin
S containing compounds	Glutathione	-
	Glucosinolate	B-D-Glucopyrinose
	Thionins	-
	Defensins	-
	Allinin	-

There is a good chance that some novel compounds will be found that demonstrate antibacterial activities. The reason for this is that several plants use secondary metabolites as a defense mechanism against microbial pathogens. Thus, plants can partially or completely mitigate the spread of microorganisms, animal, and human pathogens [23]. Advancement in high-performance screening methods allows for the detection of novel secondary metabolites, even those from well-studied plants. In addition, genetic engineering or chemically induced synthesis are used to produce vast quantities of bioactive substances [24].

Eukaryotic organelles, the mitochondria and chloroplasts evolved from bacteria through the process of endosymbiosis [25]. These processes of endosymbiosis involve the genetic transfer of material between bacteria and the host genome

CHAPTER 8

Plant Secondary Metabolites in the Management of Degenerative Diseases

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Abstract: Medicinal plants have been indispensable in the development of lead compounds for the management of human health. However, herbal remedies have not been explored maximally in modern therapeutics for the management of drug-resistant diseases, re-emerging diseases, metabolic syndrome, *etc.*

Several secondary metabolites with proven efficacious pharmacological effects have been identified from plants, some isolated but unfortunately never developed into a marketable pharmaceutical product.

Thus, this chapter provides resourceful information on the secondary metabolites of herbal plants with great pharmacological potential. Databases such as JSTOR, Science Direct, Google, PubMed, and Medline were explored for relevant information on this concept.

A spectrum of plant secondary metabolites with potent antibacterial, antiviral, antimalarial, anticancer, antidiabetic activities in different plant species were collated, the class of these metabolites and mechanism of action was compiled.

An acquaintance with efficacious secondary metabolites used in the management of various diseases will serve as a basic tool for Ethnomedical Scientists in the integration of folkloric knowledge in contemporary medicine for the formulation of herbal remedies with superior pharmacological relevance than conventional medicine.

Keywords: Antibacterial, Anticancer, Antidiabetic, Antimalarial, Antiviral, Secondary metabolites.

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1. INTRODUCTION

In recent times, the improvement of health in the society has been a challenge in most countries in the world. The availability of limited resources has soft-pedaled the effectiveness, efficiency, and equity in health gains. However, the mobilization and management of societal resources to maximize success in health management are of paramount importance. Amongst the health care needs of the society; the provision of appropriate therapeutic treatment for different diseases is of paramount importance for the promotion of the well-being of the society.

Nature has been a source of medicinal agents since time immemorial. Globally, herbal drugs have been a part of the evolution of human, civilization and healthcare for thousands of years. Folklore medicine has documented the use of plants in herbal formulation for disease management. Herbal plants were prepared using common methods such as powders, poultices, tinctures, decoctions, teas, and other types of formulations [1] until the 18^{th} century.

In the early 19^{th} century, the evaluation of herbal plant's composition began with advances in chemical analysis and organic chemistry and this has led to the isolation/ purification and characterization of several bioactive principles. This giant stride in drug discovery led to a phenomenon of innovation in the medical field. The earliest quantum leap was the isolation of an alkaloid from the plant, *Papaver somniferum* (Opium Poppy), for the formulation of the drug, morphine, in 1805.

Later in the 19th century, several drugs were formulated from plant secondary metabolites. These include salicylic acid, the precursor of aspirin produced from *Salix alba* (Willow Bark), *Erythroxylum coca*, a primary source of cocaine- a local anaesthetic, Quinine, an antimalarial drug derived from *Cinchona officinalis*, digitoxin, a cardioactive glycoside drug synthesized from *Digitalis purpurea and Digitalis lanata*, and many others with clinical relevance [2].

Over the years and even in recent times, a larger number of approved drugs are originally from herbal plants and they serve as templates for synthetic modification, and pharmacological inquest and drug precursors [3]. Thus, it is imperative to state that the use of plant products for herbal drug formulation provides the bedrock to modern therapeutic sciences and validates the initiation of a verifiable system of medicine. Several benefits of using medicinal plants include its high therapeutic efficacy, little/absence of side effects, cost-effectiveness, availability, *etc* [4].

Currently, researchers continuously adopt approaches that explore plant for the development of new pharmaceuticals [5]. The high therapeutic value of medicinal plants has been accorded to the presence of several active principles referred to as secondary metabolites. Thus, in this chapter, several secondary metabolites, the plant sources and mechanism of actions were highlighted to serve as a repository of information for further research that will link nature to modern disease management, thereby proferring solutions to several ailments.

The literature used for this chapter was obtained through an in-depth search of scientific databases such as Science Direct, Google, PubMed and Medline. The reports mostly cover the use of plant secondary metabolites in ameliorating/ treatment of selected common aliments in folklore and modern medicine from the 19^{th} century to date.

Seventy-nine (79) journal articles were retrieved using the keywords (Secondary metabolites, mechanism of action, anti-malarial, anti-diabetic, anti-bacterial, anti-viral, anti-cancer activities of plants) and utilized for the conceptualization of the chapter.

2. SECONDARY METABOLITES

Secondary metabolites are a group of chemical compounds produced by the plant cell through secondary metabolic pathways such as the shikimic acid and mevalonic acid pathways. These metabolites are not required for plant growth; they rather play a major role in plant interspecies competition, protection against herbivores, ultraviolet radiation, and microbes' response to abiotic and biotic stress [6]. It is also responsible for the colour, smell and flavour in plant products. Over the years, they have shown great pharmacological potential, served as sources of lead compounds with several biological activities utilized in disease management [7]. Plants' secondary metabolites could elicit therapeutic effects on humans by acting as neurotransmitters, hormones, endogenous metabolites, signalling molecules, ligands, *etc* [8]. Secondary metabolites include the diverse group of chemicals, which include alkaloids, glycosides, lipids amines, saponins, essential oils, steroids, flavonoids, carbohydrates *etc*. Currently, about two-hundred thousand different plant secondary metabolites have been isolated and identified [9].

2.1. Major Classifications of Secondary Metabolites

Secondary metabolites are simply classified into three main groups:

2.1.1. Terpenoids

Terpenoids are secondary metabolites with molecular structures made up of

CHAPTER 9

Bioactive Compounds as Therapeutic Intervention in Neurodegenerative Diseases

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Abstract: Neurodegenerative disorders have been implicated as the cause of many devastating diseases that are characterized by gradual loss of susceptible neurons, that are increasingly rising the prevalence of neurodegenerative diseases globally; however, therapeutics for them are lacking. There is an urgent need to develop an effective therapy that can combat the menace caused by disorders of neurodegenerative origin such as Alzheimer's and Parkinson's diseases, stroke, and traumatic brain injury. Peer-reviewed articles were explored for the purpose of this review. Several natural products from medicinal plants have been reported to have phytochemical components with bioactive effects in addition to nutritional value. An appropriate bioactive component is essential for a healthy lifestyle as it plays a significant role in the modulation of neurodegenerative diseases. This review covers the mechanism of action of neurodegenerative disorders and highlights selected classes of bioactive compounds and their effects on neurodegenerative disorders. The use of bioactive compounds in the management of neurodegenerative diseases could solve the problem of the non-availability of therapy.

Keywords: Bioactive Compounds, Disease, Intervention, Neurodegenerative, Therapeutic.

1. INTRODUCTION

Among older people worldwide, neurodegenerative disorders are a major cause of disability and premature death [1]. Among the most common neurodegenerative diseases are Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal

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dementia (FTD), Parkinson's disease (PD), stroke, and Huntington's disease (HD) [2]. Neurodegeneration is a component of numerous growth-related, devastating, hopeless illnesses that influence the sensory system and have become a significant danger to the strength of the old. The prevalence of neurodegenerative disease has become a global public health problem due to the ongoing aging situation facing western societies [3].

The incidence and damage of oxidants are termed as oxidative stress, and are referred to as pathogenic or etiological agents for diseases such as cancer, Alzheimer's, diabetes and aging [3, 4]. Such illnesses and evidence stimulated by oxidative stress have called for concern among scientists in finding antioxidants to prevent and treat such diseases [5]. Aging-related diseases have long been associated with oxidative stress. Continued dysfunction and death of neurons are characterized by neurodegenerative diseases. Oxidative stress is linked to mitochondrial dysfunction and endoplasmic reticulum, which causes apoptosis and disruption of protein synthesis in neurons. In neurodegenerative conditions, decreased activity of antioxidant enzymes such as catalase, SOD, glutathione, glutathione peroxidase means a decrease in the role of an antioxidant in neurodegeneration [6].

There is growing interest in antioxidants, especially, the naturally occurring type. Natural products are derived from the food, cosmetics, and pharmaceutical industries to include man-made antioxidants that are often limited owing to their carcinogenic potentials [1, 4]. Plants are a source of various secondary metabolites, many of which are natural antioxidants that can be considered sources of these substances, such as polyphenols, flavonoids, and essential oils [5].

The aim of this chapter is to report the beneficial role of bioactive compounds as the therapeutic intervention of neurodegenerative diseases. In this review, the discussion introduces bioactive compounds and its roles, separation and synthesis of bioactive compounds, applications of bioactive compounds, and pathophysiology of neurodegenerative diseases.

2. BIOACTIVE CHEMICALS

Currently, the use of medicinal plants in ancient times reflects the history of living particles. ‘Bioactive chemicals’ are additional nutrients commonly found in foods in small amounts [7]. Humans had no knowledge of bioactive molecules in the past, nonetheless, the use of these substances differs significantly in various ways. Natural plant chemicals are often synthesized as secondary metabolites [6]. Everyone, from a single cell to a million plant cells, makes a wide variety of survival and survival chemicals.

It is possible to break all the chemical elements of the biological system into two broad spheres. One of the main metabolites, such as amino acids, carbohydrates, lipids and proteins, are chemical substances aimed at growth and development. Other secondary metabolites, a class of chemicals that are not basic metabolites are thought to help plants improve their overall survival potential and solve environmental challenges by enabling them to interact with their environment [3].

2.1. Role and Types of Bioactive Compounds

An appropriate diet is an essential influence in a nourishing lifestyle and also plays a vital role in the inhibition of neurodegenerative diseases, including AD. The threat of dementia can be decreased by consuming a balanced diet abundant in respiratory chemicals [8]. Regardless of whether these compounds use entirely the neuro-protective impacts seen in *in-vitro* and investigations on animal species, and people under physical situations remain uncertain due to the lack of human intervention studies. There is also a lack of awareness as to whether the prices and types of chemicals contained in food make them readily available. However, their positive results have been largely confirmed by experimental studies of the epidemiological group and laboratory studies detailing the successful biological mechanisms of compound action in the mitigation of AD. Such significant improvements in selected bioactive chemicals are listed in the study. Several of these substances are in any one of the subsequent chemical categories: fat-soluble vitamins, phenolic compounds, essential fatty acids, carotenoids or isothiocyanates.

2.1.1. Phenolic Compounds

Phenolic components are present in common vegetable diets and olive oil comprising oleuropein, their most significant sources are hydroxytyrosol and oleocanthal. Oleuropein is a glycosylated seco-iridoid with several advantageous characteristics that has an important antioxidant prospect and protects nerve cells from apoptosis induced by neurotoxin [9]. It can likewise lessen the degree of Aβ and inhibit its production, and at the same time decrease the expression of glutaminylcyclase and the enzyme involved in the synthesis of Aβ. Additionally, oleuropein has a metabolic effect. Escherichia coli cell culture *in vitro* experiment showed that Oleuropein has been shown to be immune to mutant synthesis, which rapidly binds tau protein by 67% compared to the control group [3, 7].

The efficacy of wild-type tau was 79%, whereas methylene blue, the comparison tau aggregation resistor, was 75% effective. These results propose that oleuropein can evade the production of toxic tau collections, likely owing to the combination of aldehyde groups in the forms of tautomeric of its aglycone metabolite.

CHAPTER 10

Green Synthesis Application in Diabetes Therapy

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Abstract: The use of medicinal plants and or medicinal plants-aided nanoparticles (NPs) in the management of diabetes mellitus has progressively received wider acceptance over the years due to the accompanying side effects with conventional therapy. The review explores the application of green-synthesized nanostructures in the control or management of diabetes as well as probable mechanism of NPs formation and possible toxicity. Information sourced from scientific databases including Science Direct, Google Scholar, PubMed, Web of Science, SciFinder, JSTOR revealed 58 medicinal plants explored in the synthesis of four (4) NS such as gold, silver, zinc oxide and platinum with established antidiabetic potential. The NS is characterized by varying microscopic and or spectroscopic instruments such as UV-Vis, SEM, EDS, FTIR and XRD commonly are stable, smaller-sized and mostly crystalline in nature. The functional groups responsible for the reduction and stabilization of the nanoparticles are predominantly C-O, C-H, COOH, N-H found in phenols, flavonoids, alkaloids, proteins and so on. The review identified and revealed 45% studies with less than 5% (mostly from India) conducted on animal models for antidiabetic and toxicity determinations, respectively with none for clinical studies, indicating the need for intensified efforts on research on these identified plants and unidentified species for drug development.

Keywords: Diabetes management, Characterization techniques, Functional groups, Green application, Nanoparticles, Reducing and/or stabilizing agents.

INTRODUCTION

Nanotechnology is an aspect of science involving the synthesis of materials or substances in nanometer range (between 1- 100 nm) [1] or molecular level [2]. Nanoparticles (NPs), sometimes referred to as nanostructures (NS) is an evolved field whose substantial contribution to other scientific endeavours, including pharmaceutical, medicine, bioengineering, agriculture *etc*., is far-reaching [3] and multidisciplinary. In fact, a number of applications such as micro-optoelectronic

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devices, solar cells, magnetic devices, electro and photocatalytic devices, drug (gene) delivery, textile, cosmetics, x-ray imaging, biosensors, *etc*. from these domains have been generated on NPs [1, 3, 4]. Nanostructures characterized into natural or artificial are synthesized in the form of metals such as gold, silver, platinum, zinc, copper, palladium, magnetite, silicon, nickel, cobalt and or their metallic oxides and or dioxides (semiconductors), including indium oxide, ZnO, CuO, TiO_2, MgO, CaO, FeO, ZnO_2 [1, 2, 5] and or carbon, *etc*., and they are (sometimes) ascribed to different groups based on their unique properties, hence, partly the reason for the individually exhibited unique characters and well-endowed applications. Few of the features of prominent or selected nanostructures are summarized below:

Gold (Au), among other inorganic NPs was adjudged the most effective NP [6]. This could be attributed to numerous innate properties, which include but are not limited to the ease of synthesis, biocompatibility, light-scattering ability in cellular imaging, moderate susceptibility of the chemical surface functional groups, resistance to oxidation and plasma resonance, *etc.* [7, 8]. Its relevance as antidiabetic, antioxidant, anti-inflammatory and anticancer agents have been reported [6, 9 - 11].

Silver (Au) is another metal NP that has found its importance in many fields (medical, food, healthcare *etc*.) owing to its distinct features, including electrical, thermal, high electrical conductivity *etc.* [12, 13], which are linked to a number of applications such as antioxidative, antibacterial agents, drug delivery, antidiabetic, anticancer agents, *etc.* [14 - 16].

Platinum is one of the noble metals with high importance. It has been explored in nanotechnology and endowed with wide application in numerous scientific fields such as biological, medicine, chemical, electronics, *etc.* [17]. The antibacterial, antioxidant, anticancer and safety concerns of platinum nanoparticles have been reported [17].

Zinc oxide (ZnO), grouped with the like of graphene based on its unique importance and application is a metal oxide that has taken a prominent place in nanomedicine. ZnO, recognised to be the most important inorganic NP [18] due to the usefulness in biomedical, gas censors, cosmetics, agriculture *etc.* [18], is reported to possess semi conducting, piezoelectric and optical properties [19] with low toxicity and biodegradable ability, *etc.* [20]. Its relevance in nano-optical devices, nanosensors, energy storage, *etc*., has been studied by many authors [11, 19, 21].

The low toxicity and unique biological potentials exhibited by selenium (Se) placed it in the group of NPs of significance [22]. Besides, it also possesses good absorptive capability as a result of its interactions between SeNPs and functional groups (*e.g.*, amino, carbonyl, carboxylic, cyano) of proteins [23]. It is a good antioxidative and antihyperglycaemic agent [24].

Nano-synthesis Methods

Nanoparticles have continued to be developed either by top down or bottom up approaches through physical, chemical, and biological methods. While the 'top down' approach involves the breaking down of bulk material into smaller particles geared at size reduction and achieved greatly through physical processes such as milling, grinding, sputtering, evaporation *etc*., 'bottom up' approach is brought-about by the aggregation of the atoms or particles into nuclei and the eventual NS is achieved *via* chemical and biological processes including laser pyrolysis, sol gel process, supercritical synthesis, chemical vapour deposition, atomic condensation, co-precipitation, green synthesis, and so on [2]. The choice of a particular method in the synthesis of NPs is determined by the extent of toxicity, cost of manufacture, energy requirement, treatment necessity in terms of regulated pressure, temperature and pH, *etc*. Notwithstanding the above, the type or methods used in synthesizing these NPs and the adopted characterization techniques may partly determine the size, shape, and eventual characteristics and/or their pharmacological and/or biological potentials.

Characterization of Nanoparticles

The synthesis of the nanoparticles is accompanied by arrays of spectrometric and microscopic techniques such as ultraviolet-visible (UV-Vis), fourier-transform infrared (FTIR), transmission electron (TEM) or scanning electron (SEM) or fields emission scanning electron (FE-SEM), x-ray diffraction (XRD), dynamic light scattering (DLS), energy dispersive (EDS), differential centrifugal sedimentation (DCS), *etc*., which determines the point of maximum absorption and or the band gap energy, depicts the type of size (from as small as 5 nm to as big as >500 nm), shapes (cubical, spherical, triangular, irregular, pyramidal, hexagonal, octahedral, decahedral *etc*.), morphology (crystalline, amorphous, *etc*.), stability, homogeneity, surface area, and so on. The characterization aspect is germane to afford information on the system and control of the NPs [1].

Green Synthesis of Nanoparticles

Green nanotechnology is an evolving application that combines green chemistry and engineering [25] fields focusing on the reduction of energy consumption and the use of cost effective materials to produce ecofriendly materials. This type of synthesis falls into the biological method of NP synthesis using various biological substances, including enzymes, microorganisms (fungi, bacteria, algae), yeast,

CHAPTER 11

An Update on Green Synthesis Application in Cancer Therapy

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Abstract: Cancer is one of the most common health problems affecting the human population globally. One of the major focus areas that bio-nanotechnology is taking nowadays relates to nanomedicine and the use of nanomaterials in cancer therapy. Furthermore, the green synthesis of nanoparticles has been described as an effective, inexpensive, and environmentally friendly procedure. Biological organisms such as bacteria, fungi, cyanobacteria, algae, plant extracts, and enzymes and biomolecules have been reported to successfully synthesize metal nanoparticles. This review describes the types of green synthesized nanoparticles, the different green synthesis methods of nanoparticles, and their application against various cancer cell lines. Although the plant-mediated silver nanoparticle synthesis appeared to be the most common green synthesis approach used in cancer therapy, gold nanoparticles are postulated to be a better, more efficient alternative, whilst the use of zinc oxide nanoparticles is becoming an emerging trend. This review concludes that metal nanoparticles can be used as potential anticancer agents.

Keywords: Biomolecules, Cancer therapy, Drug-delivery, Metal nanoparticles, Microorganisms, Plant extracts.

1. INTRODUCTION

Nanotechnology has become a fast-growing field in the world of science and technology in recent times due to its multiple applications [1, 2]. It can be applied across a variety of fields such as optics, electronics, catalysis, biomedicine, energy science, mechanics, and the cosmetology and pharmacology industry [1, 3]. The word “nano” is of the Greek-origin, meaning extremely small; hence, nanoparticles are characterized as being relatively small in size (1-100 nm) and having an increased surface area to volume ratio [3, 4]. Generally, nanoparticles

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differ greatly in shapes (spherical, rod, and triangular) and sizes, and for the metal nanoparticles, for instance, their shapes have been reported to significantly influence their optical and electronic properties [5, 6]. The size of nanoparticles varies according to the field of application. For instance, in medicine and pharmaceutical sciences, nanoparticles synthesized for therapeutic drug delivery are often larger than 100 nm to accommodate an adequate quantity of drugs to be delivered to target tissues or organs [7, 8]. Specifically, for cancer therapy, the desired size of the nanoparticles ranges between 70 –150 nm as the arrangements in the endothelium in a developing tumour is about 100–780 nm [6]. To date, the metal nanoparticles for cancer therapy have remained a viable alternative to the conventional anticancer drugs (chemotherapy) and treatments (laser therapy, and surgery targeting tumour cells) due to several side effects such as weight loss, anemia, hair loss, fatigue, bleeding and bruising, appetite loss, diarrhea, blurred vision [7, 9]. Comparatively, cancer nanoparticle therapies, particularly those from biological sources, have been reported to be less toxic, more reliable, economical, environmentally friendly, and effective [1, 6]. Consequently, the bio-nanoscience has been employed as a potential weapon in cancer therapy.

The ultimate goal of nanoparticles is to diagnose cancer at an early stage and deliver the therapeutic agents (drugs) at an optimum dose to the right target to kill the cancerous cells. Conventional methods such as chemotherapy and radiotherapy are known for their harsh side effects and often target cells that are not specifically cancerous, resulting in the elimination of healthy cells [9]. Moreover, numerous problems in toxicity, inactivity, and limited bioassay are inferred from the weak pharmacokinetic effects of cancer medications resulting from lower solubility, stability, and metabolism. Therefore, effective formulations must be established that can address these difficulties and selectively target tumor sites without compromising the viability of healthy cells and tissues. Understanding the precise mechanism of metal nanoparticles as potential anticancer agents is also imperative. Here, various metal nanoparticles, as well as green synthesis and characterization methods, are discussed to offer an innovative possibility to examine biological units for nanoparticle synthesis and to evaluate their possible effects on cancer therapy.

2. GREEN SYNTHESIZED NANOPARTICLES IN CANCER THERAPY

Nanoparticles are desired for biomedical applications because they are essentially a bridge the gap between bulk materials and atomic or molecular structures with unique mechanistic, optic, and biology-related attributes [10, 11]. Each nanoparticle has a significant contribution to green synthesis applications. Nevertheless, metal nanoparticles are emerging as a preferred choice over conventional therapy and are being widely used in therapeutics [7, 12, 13]. Of the metals (silver, gold, zinc, nickel, iron, selenium, palladium, copper, and platinum, *etc.*) used in nanoparticle synthesis, those from silver, gold, and zinc have extensive and promising applications in cancer therapy. Hence, this section briefly highlights silver, gold, and zinc nanoparticles in both effective cancer diagnosis and therapy [8].

2.1. Silver

Silver is the most desired metal for nanoparticle synthesis due to its unique morphologies, stability, and controlled geometry [4, 14]. Silver nanoparticles (AgNPs) can be synthesized using either plant extracts or various microorganisms [6] and are being designated as most effective in the biomedical field because of their numerous applications [2, 15]. Besides their effective anti-cancer applications, studies have also implicated AgNPs as anti-parasitic, anti-septic, antimicrobial, anti-inflammatory, anti-diabetic, anticancer, and antioxidant agents [3, 5, 15 - 17]. The anticancer activities of AgNPs have been analyzed and reported against a range of cancer cells such as breast cancer, lung cancer, ovarian cancer, and human hepatoma cells *in vitro* [7]. Rattan *et al.* [18] have also reported the anticancer activity of 23 plant extracts used to synthesize AgNPs and lent credence to their being potent anticancer drug-delivery systems.

2.2. Gold

Gold is another metal that is also known to be compatible with biological material. Gold nanoparticles (AuNPs) are some of the most widely studied nanoparticles because of their surface plasmon resonance (SPR) and optical properties [15]. AuNPs can easily be synthesized, have high chemical and thermal stability, low cytotoxicity and show intense surface SPR, and can be used as drug carriers [15]. Gold nanoparticles can be prepared in a varying range of core sizes (1 to 150 nm), making it easier to control their dispersion [19]. They have a broad application range in biomedicine, such as biomolecular immobilization, leukemia therapy, antimalarial and anti-arthritic treatment, and biosensor design [20]. Furthermore, the ability of AuNPs to bind ligands (antibodies, peptides, and nucleotides) by interacting with their amine and thiols groups provides a suitable means of producing specified biomarkers and conjugating therapeutic agents [21].

The biocompatibility of soft bases like thiols and their strong interactions make it possible for AuNPs to be essential in cancer therapy [2, 21]. Due to the capability of AuNPs to inhibit proliferation induced by vascular endothelial growth factor (VEGF), they have been used to treat ovarian cancer and metastasis attributable to VEGF [22]. This submission has been substantiated *in vivo* by Bhattacharya and Mukherjee [23] in a Mouse Ovarian Tumour Model (MOT). The study found that

CHAPTER 12

Oxidative Stress Involvement in Antibacterial Therapy

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Abstract: Antimicrobial therapy is necessary to reduce the global burden of disease and infection. Oxidative stress (OS) may play a key function in determining the extent of efficacy of antimicrobial treatment regimens. However, whether the agent has a 'static' (inhibitory) or 'cidal' (killing) effect or the ability to induce an oxidative state, achieving therapy is a complex one. Bactericidal agents are known to induce a downstream cascade of responses in bacteria beyond their direct target(s). These responses correspond with the generation of reactive oxygen species (ROS) and the development of OS that eventually results in the disruption/destruction of integral components and/or processes within bacteria cells. In contrast, bacteriostatic antibiotics may not always induce cell death. Both classes of antimicrobials are useful in antibacterial therapy. The actualization of an oxidatively stressed microbial cell is key to optimizing the available antibiotic therapy options for efficient treatment and reducing the acquisition of microbial resistance. Studies are still required to expatiate on the role played by OS in antimicrobial therapy. This chapter, therefore, focuses on discussing available research data and knowledge on this complex role by OS, while highlighting potential future application and development prospects. In addition, the chapter touched OS and their sources, antimicrobial lethality-OS association, factors affecting OS-mediating therapy and efficacy, bacterial adaptations to OS in response to antimicrobial treatment and prospects for combination therapy with bactericidal agents and adjuvants.

Keywords: Oxidative stress, Reactive species, Antibiotics, Antimicrobial therapy, Bacteria, Adaptations.

1. INTRODUCTION

Antimicrobials-induced cell apoptosis is a multifaceted and complex process [1, 2]. While more effort has been directed towards the derivation or discovery of

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new antimicrobials and their specific target(s) in microbial cells, this approach is simplistic. This approach points to the view that antimicrobials evince their effects through the inhibition of specified targets only. However, the upgrades in high-throughput techniques have empowered scientific analysis into microbial responses to stress or toxic conditions [3]. In other words, microbial cell death or inhibition could be a function of more than the antibiotic-target specific theory. It may also be a consequence of affected cell processes, for example, physiological and metabolic processes, as well as interactions that transcend cell target(s), and may be associated with the development of oxidative stress (OS) in cells under treatment conditions [3]. The accumulation and excessive presence of reactive oxygen species (ROS) in a living system could culminate in oxidative stress (OS). Oxidative stress has also been defined as a state of antioxidant deficiency [4]. ROS usually target lipids, proteins, RNA and DNA [5], and their occurrence beyond optimal level is harmful to cells [6].

Generally, antimicrobial therapy faces pertinent challenges on a global scale, given the increase in antimicrobial resistance (AMR) of microbial species to available antibiotics or antimicrobial agents [7]. In a bid to tackle AMR, research should not be limited to the discovery or synthesis of novel antimicrobials and new modes of action but also extended to investigations on integral factors that contribute to the development of AMR and antimicrobial tolerance [7]. Under certain conditions, exposure of bacterial cells to some classes of antimicrobials could enhance increased production of ROS, that may cause death and disruption of the target with which the drug or agent interacts within the cells [3]. In contrast, antioxidants and OS defences could contribute to reducing susceptibility to antibiotics and be involved in bacterial responses to antibacterial or antimicrobial agents [7].

Antibacterial agents, especially bactericidal antibiotics, disrupt the bacterial cells they permeate and may cause irreversible damage or death to the cells through breakage in deoxyribonucleic acid (DNA), and induction of oxidative stress biomarkers. These effects are, however more pronounced in bactericidal agents [8, 9]. In the Fenton pathway, DNA is damaged by hydrogen peroxide (H_2O_2), a ROS [10]. It has also been reported that aerobic microbial species such as *Escherichia coli* produce significant quantities of intracellular peroxide to induce OS and cause damage to their own DNA [11].

Again, in the study of the *E. coli* metabolome, some changes were profiled in response to three antibacterial agents, that is, quinolones, aminoglycosides, and β-lactams antibiotics. *Escherichia coli* cells showed a decrease in lipid quantities, breaks in the nucleotide chain, an increase in the redox condition within cells, and upregulated levels of central carbon metabolites [12, 13]. The loss of homeostasis in the cell's metabolic state led to toxic shifts which was an evidence of OS in treated cells. Following the establishment of an oxidatively stressed state, breakage in DNA, increase in nucleotide oxidation, malondialdehyde adducts, and carbonylation of protein were also reported [8]. Hence, shifts in cell metabolism may function in the regulation of bacterial susceptibility responses [14, 15]. The disturbance of metabolic processes has been reported to stall the uptake of antibiotics [16] and induce bacterial protection by decreasing cell growth [13]. It may also downregulate the generation of by-products which are toxic to the cells [3]. Thus, microbial reactions to antibiotics used in antimicrobial treatment can be a function of several interactions that induce a stressed oxidative state in affected cells.

Considering the foregoing, increasing research insights into how antimicrobial agents impact microbial physiological and metabolic responses, as well as the OS-bacterial cell disruption link in antimicrobial therapy, could also be key to solving the nagging global challenge of AMR. This would further aid the evolution of therapeutic techniques to improve the efficacy of treatment regimens in the future. This chapter, therefore, aims to synergize a range of relevant and available information in the literature on the OS function in antibacterial therapy. Information for the chapter was derived from research and review articles and an array of online databases.

2. DISCUSSION

2.1. Sources of Oxidative Stress

Some of the known sources of oxidative stress include, but are not limited to obesity or metabolic syndrome, leukocytospermia, alcohol and tobacco usage, bacterial prostatitis; sexually transmitted disease (STDs), for example, those caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae* (Gonorrhoea), and *Treponema pallidum* (Syphilis); viral infections like hepatitis, human immunodeficiency virus (HIV), mutations that occur in microorganisms which increase OS stress levels [4], and antimicrobial agents used in antimicrobial therapy. However, the effects of ROS generation leading to oxidative stress as a mechanism of antibacterial action, the OS-antibacterial lethality link in antimicrobial chemotherapy, and bacterial mutations in response to OS and antibacterial agents are the subjects of focus.

2.2. Mechanism of Action of Antibacterial Agents

Some antibacterial agents that have shown ROS-generating capacity as a mode of

CHAPTER 13

Phytotherapy and the 'Omics Concept

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Abstract: Medicinal plants are particularly important biobanks for chemical and structural diversity and the identification and characterization of druggable agents in the pharmaceutical developmental processes. Many researchers are now striving to upgrade traditional medicine to match modern medicine. One of the greatest means to do this is by omics sciences. This chapter focuses on the description of 'omics technologies as a pivotal tool in the standardization and modernization of phytotherapy. Some of the 'omics approaches discussed are genomics, proteomics, chemoproteomics, glycoproteomics, immunoproteomics, interactomics, transcriptomics, metabolomics, toxicogenomics, pharcogenomics, pharmacometabolomics, phytochemomics, toxicometabolomics, phenomics, cytomics, and metallomics. These fields of sciences are very important for the understanding of components and mechanisms of actions of cells, tissues, organs, and systems with disease mechanisms. Thus, 'omics sciences have been gaining ground and acceptance in the drug development processes of modern medicine and as a precision medicine for disease management. Overall, utilizing 'omics technologies as tools for the standardization and modernization of phytotherapy is a promising way to improve traditional medicine in tackling several life-threatening and deadly diseases.

Keywords: Phytotherapy, Medicinal plant, Omics technology, Genomics, Transcriptomics, Proteomics, Metabolomics.

1. INTRODUCTION

The study of the use of plant extracts or extracts from another natural origin as therapeutic agents that promote the healthy living of organisms is referred to as phytotherapy or herbal therapy. It involves the use of the whole plant or parts of the plant as foods, teas, powdered herbs, liquid extracts, incense, smudges, and skin preparations to manage organisms' conditions. Examples are adaptogens, adjuvants, analgesic, antiemetics, aperients, astringents, *etc*. Adaptogens are herbs

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that are used for the improvement of the adaptability of the body to stress. Adjuvants enhance the body's response to a remedy. Also, analgesic and anodynes plants are used for pain relief in the same manners and antiemetics are used for lessening nausea and preventing vomiting. Aperients are mostly used as moderate laxative and digestion or appetite modifiers. Astringents could be used in tissue contraction and regulation of body secretion. They are also used to tighten or change the tone of the body. To mitigate or soothe inflammation, Balsamic herbs are extremely useful. Other uses of plants and plant extracts are as an expectorant, emmenagogue, hypnotics, and demulcent to mention a few. Currently, it has been reported that 38% of United States adults depend on some kind of herbal medicine as part of their alternative medicine. Being that as it is, there are a lot of concerns on their effects in the general biological system, toxicological effects, efficacy, and reproducible method of preparations, *etc*.

Historically, phytotherapy as a way of disease management is as old as the age of man on earth. The first man to use the term "phytotherapy" as a concept in 1913 was Henri Leclerc, who was a French physician. Since the beginning of the world, there was always quest to search for the rescue for human discomfort or disease. The act of using medicinal plants for different human conditions (disease states or discomfort of any form) is natural [1]. Moreover every knowledge about herbs was gained by experience. The reason for using a particular plant or plant product would be as a result of other user experiences and that was how thousands of plants become known for their roles and functions in biological system. One of the written evidence of the use of herbal terapy was found in Nagpur with a Sumerian Clay Slab about 5000 years old. It has more than 250 different plant components made up of 12 different recipes [2]. "Pen T'Sao" was written by Emperor Shen Nung circa 2500 BC. In the book, about 365 drugs were proposed from dried plants' parts. Some of these prescriptions are still in use today e.g., *podophyllum*, *Rhei rhizoma*, camphor, *Theae folium*, cinnamon bark, ginseng, jimson weed, gentian *etc* [3, 4]. In India, a book, "Vedas" described the most abundant plants for disease treatment. It is established that most numerous spice plants used until today originated from India e.g., pepper, nutmeg, clove. *etc* [5]. Also, in 1550 BC, about 700 different plant species such as willow, fig, juniper, onion, common centaury, aloe, castor oil pomegranate to mention, but few were gathered and enumerated for the bioactivity potentials [6, 7]. Other historical information about the use of herbal medicine can be found in the literature [8 - 13].

As mention above, the use of phytotherapy in the management of different diseases has been existent for centuries. Many researchers have worked on the cytotoxicity effects of several medicinal plants in the efforts to provide a cure for cancer disease. Wargovich and co-workers have reported the effect of herbs in the prevention of cancer and other diseases [14]. For prostate cancer, *Pygeum africanum*, which is commonly used in Europe and the USA for benign prostatic hypertrophy (BPH, has been proven to be very efficacious against cancer and safe for consumption at the described dosage [15]. Thus, this plant could be a good supplement for the prevention of prostate cancer. In another research *Boophone disticha*, a South African ethnomedicinal plant, was investigated phytochemically and phytotherapeutically for its usage in the management of diseases such as inflammatory disease, mental illness, and wounds healing [16]. Also, phytochemical analysis of *Genus uncaria* was carried out on nineteen species of the plant, which revealed some important pharmacological properties, including usage for rheumatism, hyperpyrexia, asthma, hypertension, *etc*., in South America, Malaysia, Africa, Philippines, and China [17]. Other applications of phytotherapy in diseases' management have been enumerated, such as liver disease [18, 19], skin disease [20], Alzheimer's disease [21], urologic disease [22], nonsurgical treatment of periodontal disease [23], Parkinson's disease [24], cardiovascular disease [25] coronavirus [26, 27], urinary stone disease [28], and cancer [29].

The different kinds of phytomedicines used in the management of various conditions are also referred to as phytotherapy. The combined approach to bridge phytotherapy and modern medicine and between available genomic information and several biological processes involve the use of the different strategies from many analytical strata in combination with sophisticated computational studies [30, 31]. Although the genomic study is very significant and impactful, it is imperative to fill the gap between the series of information for the identification and characterization of probable biomarkers with the physiological and pathological processes in the living system coupled with potential therapeutic agents [32]. The field of science responsible for this is omics science. It is relevant in the standardization and characterization of phytomedicine with correlation to genomic information. An omics concept is a vital technique in the modernization of phytotherapy. It involves technologies that measure some characteristic of a large family of cellular molecules, such as genes, proteins, or small metabolites. It is a branch of science comprised of many disciplines in biological sciences with their names ending in omics such as genomics, proteomics, transcriptomics, metabolomics, glycomics, lipidomics. It involves the characterization and quantification of structure, function, and dynamism which make up the organism. As a concept, omics science is commonly used by research and medical professionals like bioinformaticians and molecular biologists. The importance of the application of omics in phytotherapy cannot be overemphasized since it has penetrated almost all aspects of medicine.

Omics can be considered as a basis for precision medicine. The results of the data

CHAPTER 14

Phytoinformatics in Disease Management

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Abstract: The profound importance of medicinal plants as therapeutic agents as well as their economic values has captured the attention of researchers around the world. However, it has been recognized that standardization of medicinal plant research is required for its incorporation into modern medicine and to maintain the healthy development of the traditional medicine industry. Due to this fact, several extensive research efforts have been added to the existing approaches to upgrade the sector through standardization and authentication of medicinal plant and plant products as well as bioengineering of metabolic pathways. This chapter has divulged information about the application of computational omics approaches to medicinal plant research and its relevance in disease management. Omics studies such as genomics, transcriptomics, proteomics, metabolomics as well as multi-omics data integration were accounted for their application in a medicinal plant. Some bioinformatics programs, tools, and web databases were explained and their application in the phytoinformatics analysis of medicinal plant was discussed. This chapter concluded with the importance of storing, integrating, and management of biological and medicinal plant data to make them available as information used in disease management. It is, therefore, hoped that this chapter will enlighten medicinal plant researchers more on the availability of computational tools to use in standardizing traditional medicine and authenticate the methodologies by making them reproducible and applicable to disease management.

Keywords: Omics studies, Medicinal plants, Bioinformatics tools, Databases, Standardization, Plant metabolites, Disease management.

1. INTRODUCTION

Every living organism is bound to pass through both healthy and disease states at certain times in its life span. The change in the biological system from healthy to disease state quest for remedy, and this gingers the search for various sources of traditional medicines. The use of plants and plant products as remedies for human diseases dates back to time immemorial. The recognition of medicinal plants as a vital source of remedies for several human diseases came into play when modern

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medicine practitioners started questioning the safety, standardization, reproducibility of methods, and authenticity of traditionally based remedies [1]. Even though it cannot be disproved that medicinal plants are efficacious, some questions could not be answered. However, with time, the introduction of sciences into traditional medicine enlighten the dark spot in the use of ethnomedicinal plants to treat human diseases. Tradition medicine is common in Africa, India, China, Arab and other countries with western countries accepting it later after some facts have been established regarding the potency and safety of plants [2, 3]. Thus, the world depends on medicinal plants for the management of disease and other unhealthy states. The allopathic, which is widely accepted nowadays, is also based on medicines from the animal source, plants origin, and mineral resources. Medicinal plants are renewables reservoirs, safe for consumption, readily available, and cheap [4, 5]. Medicinal plants are good sources of useful chemicals with bioactive properties and so they are the most acceptable sources of drug and therapeutic agents in traditional medicines, complementary and alternative medicine, and also in the allopathic system of medicines [6]. Several ethnomedicinal plants have been proved efficacious in the management of many diseases such as neurodegenerative diseases [7], inflammatory and cardiovascular diseases [8], HIV/AIDS [9], plants' diseases [10 - 12], sickle cell disease [13, 14], cancer [15], and infectious diseases [16 - 18].

Even though medicinal plants are particularly important sources of therapeutic agents used by humans for ages, the knowledge of the vital information about the molecular, chemical, and cellular systems is just gaining ground with the invention of modern technologies and molecular biology techniques, jointly referred to as omics sciences. The advent of omics sciences enables scientists and researchers to explain complex information in genes and genomes coupled with metabolic proteins involved in biological systems [19]. Currently, in all the continents, medicinal plants have provided substantial advantages to the pharmaceutical industry in the same ways as they have provided stability to the biomedicine industry. This was possible through the establishment of pressing and urgently standardized and advanced research activities on the medicinal plants. So, in disease management, there is a need for phytochemical informatics to decipher and understand the biomarkers and bioactivities of phytochemicals. Two tasks in the applications of phytoinformatics to medicinal plant research in disease management are to provide standardization and characterization of the plant materials as well as to decipher the mechanistic annotations of the metabolic pathways of the plants' bioactivities. These applications of phytoinformatics would be accomplished through medicinal plant research using multi-omics data integration and technologies such as genomics, proteomics, transcriptomics, *etc* [20, 21]. On the other hand, phytoinformatics is combined with system biology to bridge the gap between the phytochemical information, their bioactivities, and disease management. The system biology approach is a multidisciplinary way to understand the complex processes in the human biological system. It is the combined efforts of chemists, biologists, physicists, mathematicians, and bioengineers to integrate an enormous amount of data from omics studies to arrive at a precise medicine for a disease. Reports have indicated the importance of system biology in the understanding of the regulatory and metabolic pathways networks in plants [22 - 24]. But what is disease management? The concept of cost reduction and improved life quality of individuals living with disease through total prevention, cure, and integrated care from professionals is referred to as disease management. Disease management is the way of a regulated and coordinated intervention program for the health sector. So, to be able to outline proper and accurate disease management, there is a need for integrated information from genomics, proteomics, transcriptomics, metabolomics, and other omics science to identify, characterize, and validate the targeted disease biomarkers as well bioactive ingredients from medicinal plants.

This chapter is aimed at deciphering and elucidating the phytoinformatics concept in disease management. It will include the relevance of medicinal plants in disease management, informatics from omics sciences and their relevance in disease management, phyto-bioactive chemical data integration from different databases, tools, and some computational and bioinformatics analyses to integrate Phyto-bioactive chemical data for disease management. The chapter will be concluded with further and prospective areas to be explored by the traditional medicine researchers in the phytoinformatics for increasing the standardization of the medicinal plant plant-based diseases management.

2. RELEVANCE OF MEDICINAL PLANTS IN DISEASE MANAGEMENT

In the quest for the efficacious, safe, cheap, and readily available cure and treatment for various human diseases, the human being has explored several other organismal species including plant and plant-related species. The ethnomedicinal plant has been the most important and reliable source compared to other sources of human cure and treatment; they possess various secondary and primary metabolites required by the living organisms and metabolic pathways that make up the organism [25, 26]. The metabolites modulate the pathways or cause biochemical changes that could help in the treatment of diseases. Moreover, for every plant identified for its bioactive chemicals, all parts of the plant are particularly useful. These include the fruits, seed, leaf, bark, stem, roots, flowers, all prepared in different forms depending on the diseases and method of development [27].

The use of the plant as a remedy dated back to the prehistoric era. Not only that

CHAPTER 15

Computational Applications in the Drug Discovery and Development Processes

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Abstract: The traditional drug discovery and development process has been shown to be not only time-consuming and risky, but also expensive. The identification of disease-related targets, the identification and optimization of novel leads, and drug development are the three critical steps in modern drug discovery. Approaches such as genomics, proteomics, molecular biology, cell biology, structure biology, computational biology, and bioinformatics are commonly used to identify disease-related targets. Here, we appraised the significance of computational applications in modern drug discovery and development. It was revealed that the adoption of novel computational technologies has proven to be efficient in identifying drug targets and drug candidates against degenerative diseases such as diabetes, cancer and bacterial infections, and the concept holds significant promise for a future breakthrough in drugs discovery, design and development. The challenges involved with computational applications in drug discovery are basically those of precision and accuracy in handler and software limitations. However, future breakthroughs and effective outcomes depend on the combination of advanced models with vast experience in the field of drug discovery and an understanding of the limitations of the existing computational tools.

Keywords: Bioinformatics, Computational Science, Drug Discovery, Drug Development, Life Sciences, Therapeutic Target.

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1. INTRODUCTION

Historically, medicines have often been derived from fungi, herbs, plants and other natural sources known to man [1]; the naturally derived drugs constituted those of plant, animal, and microbiological sources. Many important drugs were derived from plants, both directly and indirectly- hence, plants were deemed to be vital sources of novel pharmacologically active compounds [2]. Until the mid 19th century, there was little to no scientific understanding of why certain substances (mostly natural products) produced medicinal effects. There was also a non-existent use of man-made/synthetic drugs for disease cure. Basically, pharmaceutical drug discovery trended through a different era and commenced with the discovery of the first synthetic compound (chloral hydrate) in 1832, which was not used medically until 1969. Drug discovery from synthetic compounds of organic molecules such as citric, gallic, malic, lactic, oxalic and uric acids was rampant [3]. In the 20th century, fusion of knowledge from biochemistry, microbiology and synthetic organic chemistry yielded the production of natural, semi-synthetic, and synthetic drugs, whereas the discovery of antibiotics by Alexander Fleming aided the development of more antibiotics in order to treat infectious diseases [4]. Further advances in drugs discovery, design and development took place with the discovery of vaccines, active modified purines as anticancer drugs, and antiviral drugs [5, 6], which were greatly helped by the discovery and the knowledge of DNA Recombinant Technology. In the 21st century, multidisciplinary approaches, bioinformatics, combination chemistry and molecular modeling have aided pharmaceutical advances in drugs design and development [7].

In modern day trends, drugs discovery occurs through gaining new insights into a disease process, allowing the design of an agent(s) that stops or reverses the effects of the disease [8]. Drugs are also discovered when many tests of molecular compounds are carried out in order to observe their effects against certain diseases (Fig. **1**). The discovery of new drugs also stems from the knowledge of existing treatments that have unanticipated effects and furthermore, new technologies, these include technologies which work in the manipulation of genetic material and those that function in the specific targeting of drugs/medical products to body sites [9].

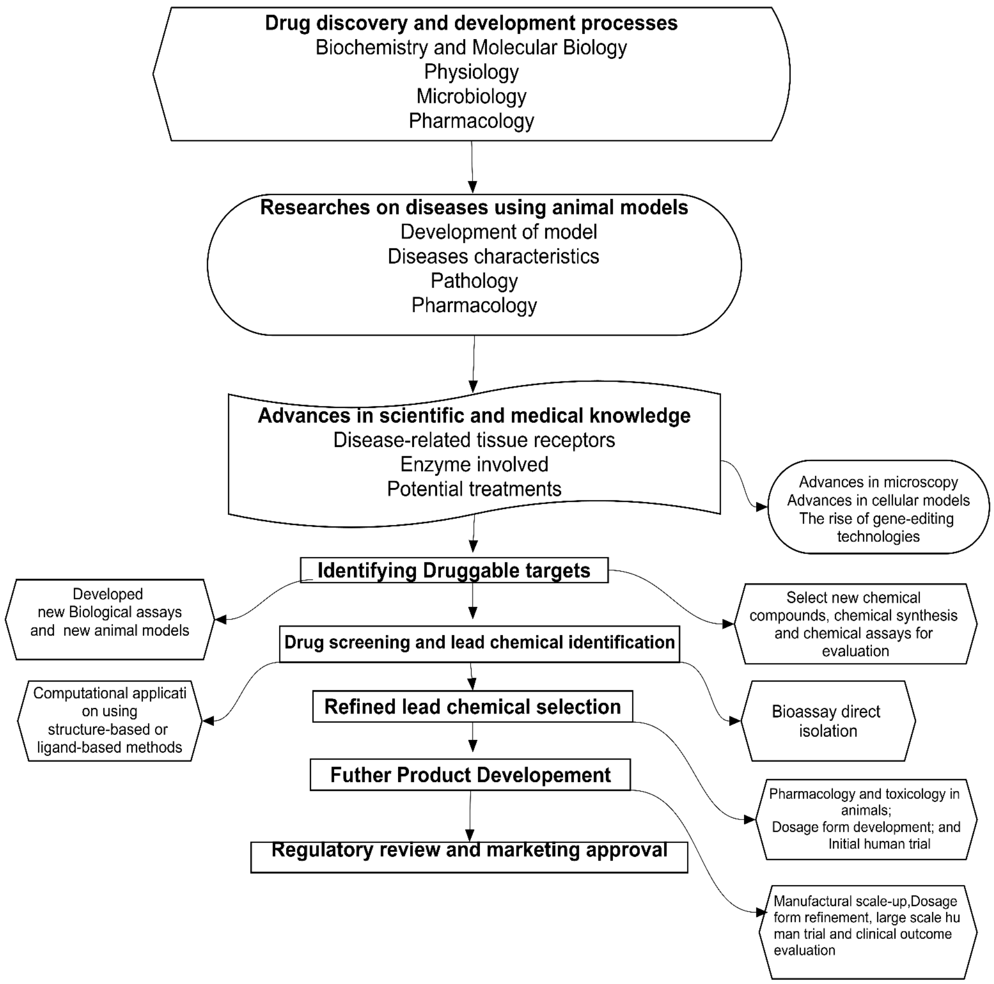

Fig. (1). Flow Chart of Drug Discovery and Development.

After identifying promising/lead compounds, experiments are carried out in the development of new drugs (Fig. **1**) to gather information on the drug's absorption, distribution, metabolism, and excretion [10]. The potential benefits of the new drug in addition to its mechanisms of action and the best dosage for effective use, are also examined. Furthermore, the method of ingestion, adverse effects, toxicity, and the drugs' interaction and effectiveness in comparison with other drugs are observed and studied [7, 10] to gather information on the absorption, distribution, metabolism and excretion of the drug [10]. They also examine its potential benefits and mechanisms of action in addition to the best dosage for effective use.

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