THERAPEUTIC INSIGHTS INTO HERBAL MEDICINE THROUGH THE USE OF PHYTOMOLECULES

Editors:
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(Volume 3)

Therapeutic Insights into Herbal Medicine through the Use of Phytomolecules

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PREFACE

Plants are a source of a wide variety of natural products with a variety of medicinal characteristics that are always being researched to create new medications. Today, the majority of pharmaceutical drugs are made from these natural ingredients. Plants produce a vast array of chemically diverse secondary metabolites with specific biological activities, but their molecular mechanism, pharmacokinetic profile, and safety have not yet been fully analyzed. Natural product research is experiencing a remarkable resurgence of interest in this age of rapidly advancing science and technology, and the findings are quite intriguing. Current research is gaining renewed attention for its ability to produce novel and intriguing scaffolds with improved physicochemical, pharmacokinetic, and pharmacodynamic properties. However, it is still challenging to analyze the mechanisms of action of herbal medications on a holistic level due to the complexity of substances and their linked various targets of traditional herbal medicine. Additionally, ADME (absorption, distribution, metabolism, and excretion) properties are described as the dynamic alterations in drugs within the body, which are critical in drug discovery and development. The discovery and development of drugs based on natural products are challenging tasks that require a highly integrated interdisciplinary approach. Recent technological innovations, scientific advancements, and research trends all point to the fact that natural products will continue to rank highly as a source of novel medications in the future. Volume 3 (Therapeutic Insights into Herbal Medicine through the Use of Phytomolecules) of Natural Medicine includes different chapters that offer important information about the screening of phytoextracts/phytomolecules for drug discovery.

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CHAPTER 1

Pharmacological Potential of Bioactive Phloroglucinol Compounds of the Plant Kingdom

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Abstract: Historically, natural products, which are substances generated by living organisms found in nature, have made an important contribution to pharmacotherapy, especially those from plant sources. Phloroglucinols are significant bioactive polyphenolic compounds that are found in plants, marine and microbial sources. Their chemical structures include an aromatic phenyl ring with three hydroxyl groups and are usually made of two or more rings linked together through methylene bridges. They exist widely in several plant families and are known for their significant biological potentials, such as antibacterial, antifungal, anti-inflammatory, antileishmanial, antiplasmodial, antiproliferative and cytotoxicity activities. This book chapter provides an overview of phloroglucinol compounds in the world, their location in the plant, and their pharmacological applications.

Keywords: Biological activity, Medicinal plants, Natural products, Phloroglucinols, Phytomedicine.

INTRODUCTION

Since time immemorial, mankind has searched for medicines to prevent and cure various diseases and also to get rid of pain. These medicines are generally compounds derived from natural resources such as animals, marine organisms, microorganisms, or plants. Among these sources, plants have been broadly recognized as a tremendous source of medicinal compounds for the preparation of drugs [1].

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According to the World Health Organization, up to 80% of the world's population continue to depend on plants for their medicinal properties [2, 3]. Plants have different chemical compounds, including secondary metabolites, which are found in many families of the plant kingdom, and have been reported to possess several biological properties with various applications in industries, such as pharmaceutical industries [4 - 6]. Phloroglucinol derivatives, mostly found in the Myrtaceae family, are of interest because of their scaffolding structure and biological activities. The literature review indicates 700 naturally occurring phloroglucinols, including synthetic or semi-synthetic ones with a vast array of activities. Phloroglucinol Mylan and Spasfon are used worldwide as antispasmodic drugs that fight against abnormal and painful contractions [7].

Knowledge of these natural compounds in regard of their interesting activities can greatly contribute to the success of natural medicine management today and in the future.

In this chapter, we present what phloroglucinols are and the bioactive phloroglucinol compounds studied for their phytopharmacological potential. We also review the classes of phloroglucinols and their localization in the plant.

OVERVIEW OF PHLOROGLUCINOL COMPOUNDS

Definition

Phloroglucinol is a class of natural products containing 1,3,5-trihydroxy benzene (**1**) as the basic skeleton and the simplest member (Fig. **1**). It is a colorless and odorless solid which was first isolated as a hydrolysis product of glucoside phloretin obtained from the bark of fruit trees. The phloroglucinol family, displays a large range of interesting biological activities and consists of more than 700 naturally occurring derivatives [8].

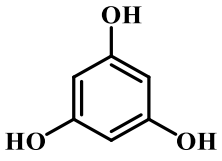

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Fig. (1). Chemical structure of 1,3,5-trihydroxy benzene.

Phloroglucinol as a Scaffold in Biology

Among the natural products, we have phloroglucinols, which are found in the form of derivatives such as anthocyanidins, catechins, coumarins, flavones, and glucosides. Some of these natural products have very interesting bioactivities and potential medical applications, as described in the next title [7].

Phloroglucinol Derivatives

Bioactive phloroglucinol compounds have been reported from diverse natural sources such as marine, microorganisms and plants. Phloroglucinol derivatives are a main class of secondary metabolites that we find in the Myrtaceae family as well as in several other families. In this book chapter, we have classified phloroglucinols into:

- Monomeric,
- Dimeric,
- Trimeric,
- Tetrameric and higher,
- Phlorotannins.

We will particularly extend our chapter on monomeric and dimeric phloroglucinols [7].

Monomeric Phloroglucinols

Numerous monomeric phloroglucinols are reported to be present in plants as well as other natural sources and have been revealed to have several biological activities. Acyl phloroglucinols, phloroglucinol–terpene adducts, phloroglucinol glycosides, halogenated phloroglucinols, prenylated/geranylated phloroglucinols, phloroglucinols linked to an α -pyrone ring and cyclic polyketides are the different subclasses of the phloroglucinols. We will partially discuss these subclasses in the following sections.

Acyl Phloroglucinols

Among the number of acyl phloroglucinols which exist, only simple ones have been described, such as acyl phloroglucinols with a prenyl/geranyl moiety or with a pyran/furan ring skeleton, phloroglucinol terpene adducts and dimeric/trimeric acyl phloroglucinols Fig. (**2**). Acyl phloroglucinols are reviewed according to the variation in acyl functionalities, and the most known is grandinol (**2**), which is a phloroglucinol derivative obtained from mature leaves of *Eucalyptus grandis* and containing isovaleryl, formyl and methyl substituents [9].

CHAPTER 2

Raging the War against Rheumatoid Arthritis with Plant-Derived Products: Skepticism to Clinical Development

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Abstract: Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disease manifested by progressive articular and extra-articular disabilities. Pieces of evidence hint that tremendous research efforts have increased the likelihood of attaining a better treatment goal. However, the associated risks, drug failures, and high costs of the available drugs or regimens still limit their widespread use. Even though natural products are rarely considered for lead identification, which is counterintuitive to traditional drug development, natural products occupy a large chemical space, unlike synthetic screening methods. Although skepticism towards the use of natural products continues, the growing attention of researchers towards the diverse flora has led a plethora of molecules and therapies to reach clinical trial settings. This chapter sheds light on the challenges in the development of plant-derived compounds or therapies for the management of RA. It discusses the plant-derived products (including diet-based therapies) undergoing clinical development for the treatment of RA.

Keywords: Dietary therapy, Herbal therapy, Natural products, Plant-based products, Phytochemicals, Plant supplements, Rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease manifested by progressive and chronic articular disabilities that further exhibit extra-articular manifestations such as vasculitis, rheumatoid nodules, rheumatoid lung, uveitis, keratoconjunctivitis sicca, pericarditis, and systemic comorbidities [1 - 4]. Besides the direct medical expenses, RA results in individual as well as socio-economic

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burden as a consequence of reduced physical functioning, poor quality of life, and higher comorbidity risk [5]. Despite advances in research and efforts to understand the cascades of RA pathogenesis, several questions remained unanswered. Similarly, the existing pharmacological therapies either failed to show the desired responses or exhibited only partial effects. In addition, these therapeutics are rarely capable of achieving sustained remission and require prolonged treatment options. Reliable predictive tools for prognosis are still lacking [6]. Considering the treatment-associated toxicities and expenses of therapeutic modalities, alternative options are needed for the effective treatment of RA.

Since ages, plants and plant-derived products have represented a diverse source of active molecules for the treatment of various chronic diseases, including RA. For instance, several preclinical studies have reported chemical classes like alkaloids (*e.g.*, piperlongumine and sinomenine), carotenoids (*e.g.*, β-cryptoxanthin), flavonoids (*e.g.*, kaempferol and luteolin), polyphenols (*e.g.*, resveratrol), anthraquinone glycosides (*e.g.*, emodin), *etc.* to possess a mitigating effect on RA (discussed in detail in subsection 5.2). Notably, the majority of these interventions appear to be focused on the suppression of RA-associated inflammation or the prevention of autoimmune conditions. Considering the potential correlation between modifiable risk factors and the alleviation of RA symptoms, several clinical trials are underway to assess the impact of dietary interventions on disease progression in RA patients. However, the fact cannot be denied that there exist lacunae in the knowledge of mechanistic insights into dietary therapy on RA-specific pathways. Fascinatingly, scientific evidence encourages researchers to exploit the health benefits of dietary therapy-more precisely, a vegan diet consisting of only plant-based foods [7]. This chapter discusses the basic pathogenesis of RA, followed by a detailed review of the plant-based products and diets undergoing preclinical and clinical development in search of potential interventions for RA.

PATHOGENESIS OF RHEUMATOID ARTHRITIS

RA is believed to be influenced by environmental factors, genetic predisposition, or both; however, the exact causes still remain obscure [8]. Over 100 genetic loci are implicated in the immune mechanisms involved in the risk and progression of the disease, including major histocompatibility complex class II loci (*e.g.*, human leukocyte antigen or HLA system), post-translational enzymes, and components of intracellular regulatory and co-stimulatory pathways [8, 9]. Involvement of additional factors, including obesity, vitamin D deficiency, periodontal disease (caused by *Porphyromonas gingivalis*), exposure to silica dust, cigarette smoking (particularly in HLADR01/04^{+} subjects), *etc.* has also been evidently reported [4,

10]. Importantly, seropositivity for rheumatoid factor or RF (autoantibodies against immunoglobulin G) and anti-citrullinated protein/peptide antibody (ACPA) due to immune dysregulation are considered the distinctive features of RA [11 - 14]. Due to the heterogeneous nature, discussion on detailed pathogenesis is beyond the scope of this chapter. (For detailed insight into pathogenesis, please refer to the given references [4, 5, 15, 16]).

For instance, articular damage and disease progression are most likely to be associated with the complement activation triggered by the complex formation of ACPAs with citrulline residues on self-proteins like type II collagen, histones, fibrinogen, fibronectin, vimentin, and α-enolase. The ACPA-generating B cells are found in the circulation and the synovium [17, 18]. ACPA promotes bone erosion either by initiating osteoclast activity *via* vimentin binding, Fc-receptor activation, or macrophage activation *via* Fc-receptor and/or toll-like receptor binding. As evident, effective therapy can decrease both ACPA and RF concentrations. Even though patients may completely become RF seronegative, patients with ACPA seronegativity are quite rare [19]. Similarly, the ACPA-positive RA subset is more aggressive as compared to the ACPA-negative RA subset [20]. Nevertheless, ACPAs are hypothesized to form immune complexes that further interact with RF, which directly leads to immune activation and potentiates inflammatory responses [21]. An aggressive inflammatory response followed by osteoclastogenesis and increased catabolism of chondrocytes promotes joint destruction. Clinical interventions revealed interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and probably granulocyte-monocyte colony-stimulating factor (GM-CSF) to be the major components of the inflammatory milieu [22]. In the synovium, activated fibroblasts and other activated immune cells trigger osteoclastogenesis *via* receptor activator of nuclear factor kappa B ligand (RANKL). Ultimately, it initiates bone erosion at the junction between cartilage, bone, and periosteal synovial membrane insertion. Simultaneously, cytokine-stimulated chondrocytes damage the cartilage, while matrix metalloproteinases (MMPs) degrade the cartilage matrix. Several intracellular signal transduction mechanisms are potentiated by the cytokines through the activation of cognate receptors and aggravate the inflammation-mediated damage [5].

CONTEMPORARY TREATMENT STRATEGIES AND THEIR LIMITATIONS

Following the diagnosis of RA, it is necessary to initiate prompt, continuous, and targeted therapy in order to prevent progressive joint damage or associated disability. The expected therapeutic outcomes include a significant reduction in disease severity or achieving full remission [23]. Until the early 1990s, the

CHAPTER 3

Recent Updates in Natural Product Research and Novel Approaches to Drug Delivery Using Phytomolecules

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Abstract: Herbal medicines are gaining popularity in the modern world for their ability to treat a wide range of ailments while having fewer side effects and greater therapeutic properties. However, there are many limitations when it comes to delivering active phytomolecules to the target site, including solubility of ingredients, susceptibility to degradation in the presence of gastric and colonic acidity, diminished metabolic efficacy attributable to gut microflora, inadequate absorption across the intestinal epithelium, suboptimal active efflux mechanisms, and susceptibility to first-pass metabolism. As a result, medication concentrations in the blood are below therapeutic levels, resulting in reduced or no therapeutic impact. With the rising popularity and potential therapies of herbal medicines over the last several decades, there has been a lot of attention paid to the new drug delivery method of active phytomolecules. Novel herbal drug carriers treat certain diseases by precisely targeting the diseased zone within a patient's body and delivering the medication there. Novel drug delivery systems have the benefit of administering herbal medicines at a preset rate and at the site of action, reducing adverse effects and increasing drug bioavailability. Controlling drug distribution in new drug delivery technology is accomplished by integrating the drug into a carrier system or altering the drug's structure at the molecular level. The integration of herbal drugs into the delivery system facilitates improvements in solubility, stability enhancement, toxicity mitigation, potentiation of pharmacological activity, optimized distribution among tissue macrophages, sustained release kinetics, and protection against physical and chemical degradation, thereby aligning with key principles in pharmaceutical formulation. The purpose of this chapter is to offer an

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overview of several forms of novel drug delivery systems that incorporate active components, as well as their potential therapeutic and clinical benefit.

Keywords: Herbal medicine, Herbal extract, Novel drug delivery system, Nanoparticles, Therapeutic effects.

INTRODUCTION

Plants have been considered as a source of medicine since ancient times and their traditional ways of practices are still continuing mostly in rural areas. These traditional and natural pharmaceutical aids are always accepted as primary health remedies by the villagers, where modern medicine treatments are the secondary choices. In the current scenario, active constituents derived from plants are considered prominent alternatives for synthetic pharmaceutical agents. Active pharmaceutical constituents of plants are known as phytomolecules, which can be derived from plants as secondary metabolites [1]. In today's world, scientists have been heavily involved in the study and development of innovative approaches to administer phytomolecules to the targeted site [2]. Pharmaceutical active constituents of plants are at the core of traditional therapeutic systems that have been used since antiquity [3]. Herbal dosage forms have developed from basic mixes and tablets to highly complex technology-based medication delivery systems as science and technology have progressed in the field of drug formulation technology [4]. Natural sources accounted for 90-95% of medication ingredients in ancient times. According to data on medication sources, natural compounds account for half of all pharmaceuticals used today. The escalating popularity of herbal medications in contemporary therapeutics is attributed to their potential for disease management with diminished toxicity and enhanced therapeutic efficacy. The application of advanced pharmaceutical technology in the delivery of herbal or plant-derived products has notably advanced drug product stability. Additionally, it has mitigated pre-systemic metabolism and toxic effects resulting from non-targeted drug accumulation and elevated patient compliance by facilitating ease of drug administration and enhancing overall acceptability [5]. The multiplicity of active ingredients makes developing innovative medication delivery systems for herbal products extremely difficult [6]. As a result, innovative drug delivery methods that can shield the medication from various distractions in the body, such as acidic pH, metabolic processes, *etc.*, should be developed to improve drug bioavailability. As a result, for an improved therapeutic result, it is essential to include phytomolecules in novel drug delivery systems [7].

HERBAL DRUG DELIVERY SYSTEM: SCOPE AND CHALLENGES

Over the last few decades, scientific society has paid enough attention toward the development of novel drug delivery systems for herbal medicines. Scientists have chosen drug delivery carriers with ideal characteristics in it. A novel delivery system should have two basic characteristics. Firstly, the carrier should deliver the drug at a specific rate needed by the body over the time of treatment. Secondly, they should carry the drug to the required part of the body for action. The conventional form of dosage has some significant drawbacks, such as being time-bound, unstable, taking a long time to work, liver metabolism, *etc.* In light of these disadvantages, new methods of drug delivery have been developed in order to increase the efficacy of herbal drug formulations. Different phyto-formulations have been developed that have a number of advantages over conventional dosage forms for herbal medicines, including reducing pre-systemic degradation, reducing side effects for accumulation of the drug in untargeted areas, stability enhancement, improving distribution within the tissue, sustained delivery, protection from physical and chemical degradation, improving the administration of drugs, *etc* [8].

Numerous innovative drug delivery systems have been developed to efficiently deliver herbal drugs to diverse sites within the body. These systems encompass a range of formulations, including mouth-dissolving tablets, nanoparticles, microspheres, liposomes, phytosomes, ethosomes, transfersomes, proniosomes, and transdermal drug delivery systems. Mouth-dissolving tablets play a crucial role in ensuring the high concentration of drugs in the bloodstream, bypassing the liver's first-pass metabolism. In contrast, liposomes, as biodegradable vehicles, exhibit the capability to transport both hydrophilic and hydrophobic materials, finding primary application in cancer treatment. Phytosomes represent bioavailable complexes that can effectively bypass lipid-rich biomolecules, facilitating targeted delivery within the body. Niosomes, on the other hand, characterized as multilamellar vesicles constructed from alkyl or dialkyl polyglycerol surfactants, contribute to versatile drug delivery. Proniosomes, water-soluble carriers coated with surfactant, can be easily hydrated to form niosomes, enhancing their therapeutic potential. Transdermal drug delivery systems offer a valuable means for both topical and systemic delivery through the skin. Each of these drug delivery systems presents unique advantages and applications, contributing to the expanding landscape of pharmaceutical science. This diverse array of formulations demonstrates the ongoing efforts to optimize drug delivery for improved efficacy and targeted outcomes [9].

Herbal drug delivery systems have huge potential because of their advantages over conventional systems of medicine. The medicine, which was previously not

CHAPTER 4

Molecular Basis of Therapeutic Action of Flavonoids

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Abstract: Herbs have been an integral part of human life for ages. Modern allopathic drugs had an upper hand over traditional medicine in the past century due to their mounting inefficacy, resistance, cost, and adverse effects that have led to the reclaim of herbs once again. Herbs holistically confer biological activity due to the presence of phytochemicals, which are classified broadly as carbohydrates, lipids, terpenoids, alkaloids, polyphenols, and essential and volatile oils. In this, polyphenols are a vast group further comprising flavonoids, phenolic acid, stilbenoids, tannins, lignans, xanthones, quinones, coumarins, phenylpropanoids, and benzofurans. Of this, flavonoids are hydroxylated phenolic substances with basic C6-C3-C6 rings substitution, which gives rise to a series of compounds namely, flavonols, flavanones, flavones, anthocyanidins, flavanonols, chalcones, isoflavones, and flavanols. They are abundantly found in vegetables and fruits and exhibit antioxidant, free-radical scavenging activity, anti-cancer, cardioprotective, anti-diabetic, anti-inflammatory, anti-allergic, and anti-microbial action. The advent of modern molecular techniques and computational methodologies has thrown light on the molecular mechanism of action of these flavonoids, which was otherwise obscure. Hence this chapter aims to review the types, sources, chemistry, and molecular mechanisms of action of the various phytomolecules of flavonoid groups.

Keywords: Phytomolecules, Flavonoids, Molecular mechanism Pharmacological action.

INTRODUCTION

Phytochemicals are chemical constituents of plants that confer protection to plants against pathogen chemicals, radiation, drought, and stress [1]. They are synthe-

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sized and stored in various parts of plants and are multifunctional in nature [2]. The phytoconstituents are classified as primary or secondary metabolites. Primary metabolites are sugars, amino acids, proteins, purines, and pyrimidines of nucleic acids and chlorophylls. Secondary metabolites include alkaloids, terpenes, phenolics, lignans, plant steroids, and saponins [3].

Tannins

Tannins are high molecular weight polyphenolic compounds. Gallotannins, ellagitannins, complex tannins, and condensed tannins are the four types of tannins. They are distributed in fruits such as grapes, persimmon, blueberry, tea, chocolate, and legume grasses. They are used for the treatment of diseases like rhinorrhea, leucorrhoea, and diarrhea [4].

Alkaloids

Alkaloids contain heterocyclic nitrogen atoms with a bitter taste. They are classified as pyrrolidine, pyridine piperidine, and isoquinoline alkaloids. They confer protection to plants against bacteria, fungi, insects, and herbivores owing to their bitter taste. Thus, pharmacological activities include anti-malarial, antiarrhythmic, anti-diabetic, anti-hypertensive, and anti-cancer actions [5].

Terpenoids

Terpenes are constituents of essential oils and are of commercial importance as flavoring agents in the foods and fragrances cosmetics industry. They consist of several isoprene units and are classified as hemiterpenoids, monoterpenoids, sesquiterpenes, diterpenes, and tetraterpenoids. Terpenoids possess anti-inflammatory, antioxidant, antiaging, neuroprotection, immunoregulation, anti-cancer, and antimalarial activity and are used to treat hypoglycemia and cardiovascular diseases [5].

Saponins

Saponins are triterpenoid glycosides with a bitter taste. They are abundantly found in legumes (beans and lentils), onion, garlic, asparagus, oats, spinach, sugar wheat, tea, and yam. They exhibit membrane stabilizing, immune stimulant, antioxidant, antimicrobial, antidiabetic, lipolytic, and anti-cancer properties [6].

Phenolic Compounds

Polyphenols are colored secondary metabolites present abundantly in plant-derived foods [7]. Based on the chemical structure of polyphenols, they are classified as phenolic acids, flavonoids, and nonflavonoid compounds according

to their chemical structures [8]. Phenolics in plants play an important role in plant defense against pathogens and herbivore predators. Phenolics act as phytoalexins, antioxidants, nutraceuticals, anti-cancer, and anti-inflammatory agents and prevent heart ailments. These flavonoids constitute the largest group of plant phenols with nearly 4,000 flavonoids [9]. The aim of this chapter is to review the

types, sources, chemistry and molecular mechanism of action of the various phytomolecules of flavonoid groups.

CLASSIFICATION OF FLAVONOIDS

Flavonoids consist of a diphenyl propane skeleton, with 15 carbon atoms and two six-membered rings linked to three carbon units and may or may not be connected to a third ring. Two benzene rings (ring A and B) are present in the third heterocyclic oxygen-containing (pyrene ring C). Based on the structure of the C ring and its functional groups, and the position of attachment of the B ring to the C rings, 8 subclasses of flavonoids are defined namely flavones, flavanonols, flavonols, flavanones, flavanols, isoflavones, chalcone, and anthocyanins. Studies show that hydroxyl group and α, and β ketones impact the bioactivity of flavonoids [9].

1. Flavonols such as quercetin, myricetin, kaempferol, fisetin, rutin, and isorhamnetin are distributed widely in foods such as onions, tomatoes, kale, saffron, lettuce, berries, grapes, apples, tea, and red wine [10].

2. Flavanones are widely present in all citrus fruits such as oranges, lemons, and grapes and contribute to the bitter taste of juice and its peel. The major compounds are hesperetin, hesperidin, naringenin, and eriodictyol [11].

3. Flavones are widely distributed in flowers, fruits, and leaves of red peppers, celery, parsley, chamomile, mint, and ginkgo biloba. The most studied flavones are luteolin, apigenin, baicalein and tangeritin [12].

4. Anthocyanins are present in the outer cell layers of fruits such as merlot grapes, raspberries, cranberries, red grapes, strawberries, blueberries, bilberries, and blackberries. The most commonly studied anthocyanins are malvidin delphinidin, cyanidin, pelargonidin, petunidin, and peonidin [13].

5. Flavanonols: Taxifolin is a subclass of flavanonols. It is abundantly found in olive oil, grapes, citrus fruits, and onions [14].

CHAPTER 5

Research Outcomes of Natural Products in Diabetes Mellitus

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Abstract: Diabetes mellitus, is a chronic condition with dysregulated glucose levels and has been affecting a larger global population. The disease, if not controlled, can lead to several microvascular and macrovascular complications that will impede the patients' physical and mental well-being in addition to its economic burden. Many diabetic patients are unaware of the complications and hesitate to take medicines in the early phase of the disease condition. Furthermore, many patients have limited access to conventional antidiabetic drugs, which drives the search for newer agents or relying on alternative/complementary medicines. Ancient systems such as Ayurveda, traditional African and Chinese medicine, Japanese Kampo medicine, and other systems of medicine have identified many herbal/plants, and mineral-based agents for treating diabetes. Many such plants probably more than 800 and their extracts have been scientifically proven or tested using various experimental models of diabetes in animals. Despite several *In vitro* and *In vivo* studies reporting the effects of extracts of plants on blood glucose, only a few trials have been performed to validate their efficacy in treating humans with diabetes. An apparent mismatch in outcomes was observed while translating the effectiveness of these plants from an experimental animal study to a human study. These inconsistencies among animal and human studies were remarkable in some cases. There are several aspects responsible for these variations, such as variation in plant parts/extracts, dose, duration in different studies, the difference between animal models and human disease, and initiation of drug treatment in animal model, which is generally before the induction of diabetes or immediately after the induction of diabetes. This chapter focuses on the animal studies and human clinical trials conducted on plant-based extracts and other natural products and the outcomes in controlling or managing diabetes mellitus.

Keywords: Animal studies, Clinical trials, Diabetes mellitus, Herbal products.

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Raja Chakraborty & Saikat Sen (Eds.)

INTRODUCTION

Diabetes mellitus is a metabolic disorder featuring elevated blood glucose levels, deficient insulin production and or reduced sensitivity to insulin action on cells and is also one of the predominant causes of death [1]. The major types include Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) and gestational diabetes mellitus. Type 1 diabetes in children and adolescents occurs primarily due to the destruction of beta cells and is manifested by deficient production of the hormone insulin in the human body. In this case, the administration of insulin is necessary daily, for controlling the glucose level. Type 2 diabetes mellitus is manifested by reduced secretion of insulin due to dysfunctional beta cells, or insulin dysfunction due to reduced sensitivity [2]. Of the major types, Type 2 diabetes has been reported to be most common accounting for 90-95% of the patient population. According to the International Diabetes Federation (IDF) report in 2021; the estimated diabetic population was 537 million adults and was projected to rise up to 783 million adults by 2045 [3]. In general, the strategies to treat Type 2 diabetes include control of diet, physical activity, anti-hyperglycaemic agents and lipid-lowing agents [4]. Various classes of synthetic drugs currently employed are sodium-glucose co-transporter-2 inhibitors [5], dipeptidyl peptidase-4 inhibitors [6], glucagon-like peptide 1 analogues [7], sulfonylureas, thiazolidinediones, and biguanides [8]. These synthetic agents are considered important and have made significant progress in controlling blood glucose levels *via* different mechanisms and include the use of insulin for many years. However, successful reversal of the complications is less evident and is reported for its side effects. The disadvantages include drug resistance, adverse effects, and toxicity. It is reported that sulfonylureas lose their effectiveness when used for a longer duration of years in approximately 44% of patients [9]. Hence, the search for alternative agents has been observed with the availability of natural sources, particularly from herbs.

Natural products of plant origin have been a potential source for lead compounds in drug discovery due to their rich source of active constituents for various ailments [9, 10] including diabetes [11] which has been recognised by the WHO Expert Committee on Diabetes Mellitus in its report. The scientific basis for the exploration of plant-based agents is due to the vast chemistry, along with the indications due to the use as folk medicines; the overarching aim is to establish a rationale for the use of the familiar traditional medicines, identifying active constituents and developing standardised products or identifying lead molecules that would be useful in developing new therapeutic agents [12]. It is also reported that a significant population with diabetes has inadequate access to medicines due to affordability and availability constraints; this is applicable to insulin and a range of drugs used in type 2 diabetes treatment [13 - 15]. Thus, an additional

basis for the investigation of natural products is to increase the accessibility of anti-diabetic agents to populations.

Commonly Used Plants with Proven Anti-Diabetic Activity

The prevalence of diabetes mellitus is a global health problem and diabetic-related death is increasing. Poor control of blood glucose leads to profound health effects. Regular anti-diabetic agents are helpful, however, obvious side effects have also been reported. Phytotherapy has existed for a long and over the years many attempts have been made to use herbs in the treatment of diabetes. This section deals with some examples of medicinal plants with proven anti-diabetic activity.

Momordica charantia L.

Momordica charantia L. (*M. charantia*), from Cucurbitaceae (Fig. **1**), is extensively spread along tropical territories in the globe. The fruit is a common vegetable and consumed for several centuries whereas, the plant parts are used to control blood glucose in treating diabetes mellitus. The phytoconstituents include flavonoids, triterpenes, saponins, proteins, polysaccharides, ascorbic acid, and steroids. The biological activities reported include antihyperglycaemia, antitumor, antibacterial, antiviral, anthelmintic, immunomodulation, antioxidant, anti-inflammatory, anthelmintic, antimutagenic, antiulcer, antilipolytic, antifertility, hepatoprotective and anticancer [16, 17].

Fig. (1). *Momordica charantia* L.
By H. Zell - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=10702040

CHAPTER 6

Exploration of Plant Phytomolecules' Potential for Antiviral Activity

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Abstract: Viral infections are increasing continuously, and we do not have proper treatment. Currently, the COVID-19 pandemic is an emerging threat globally. If we look into the Indian perspective against COVID-19, plant-based medicine available in ancient literature has been used, like Charaka Samhita and current ayurvedic pharmacopeia. Many viral diseases will come in the future, for which, there is a need to establish concept-based treatment with scientifically-proven pharmacological action. The plant's primary and secondary metabolites are responsible for pharmacological activities. Many plants have shown their efficacy in viral infections through their phytochemicals. In this chapter, we have conceptualized the same and identified the plants with their metabolites, which can be a direction for future research on viral disease. Currently available allopathic treatments have efficacy but toxicities too.

For a better understanding of the diseases, the pathophysiology of the same is one of the components, as it gives a complete idea about how the viruses affect us. In the Indian traditional drug system, many folk medicines are available that need to establish the correlation with the targeted sites for a disease, which can give us the direction for future viral infections. The urgency is also to standardize these drugs for proper use among the global population. For identification, isolation of primary and secondary metabolites can help in treatment and drug targeting. The beauty of traditional medicine is that it is affordable because of its availability in different regions across the globe.

Keywords: Viral infections, Metabolites, Traditional drugs, Pharmacological activities.

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Raja Chakraborty & Saikat Sen (Eds.)

INTRODUCTION

Recent waves of the COVID-19 pandemic explained to us that viral diseases are contagious and can affect the global population within a short duration of time. The drawbacks include replication and mutation. The global concern is the need to develop methods for the detection of these viruses and treatment for the same. Many treatment methods are available in the traditional drug system for viral diseases, and we need to explore the same through the available scientific data. Ayurveda knowledge is essential for the better understanding of phytoconstituents and the type of chemical constituents present in them. The metabolites of plants are responsible for their therapeutic efficacy and are being used in various viral diseases since ancient times.

VIRAL DISEASES

Viruses are infectious agents that consist of a genetic map based on genetic material (DNA or RNA). Virus nucleic acid is always packaged in a protein coat, or capsid, which consists of multiple protein subunits. The combination of nucleic acid and the surrounding protein capsid is often called the nucleocapsid [1]. All viruses have a coating of protein that gives a protective mechanism. Viruses attach to the cells and use components of the cells to help them multiply; this process often damages or destroys infected cells.

A viral disease is any illness or health condition caused by a virus. For understanding, we can classify these viral diseases according to their findings in the human body system.

Respiratory System-related Viral Infection

These diseases are highly contagious, and they commonly affect both the upper and lower respiratory tract. In the later stages, they can also cause bacterial infection; if not treated well, they can lead to death. Clinical symptoms of these viral diseases are sneezing, cough and cold, and sometimes, body aches.

These symptoms are mainly seen in respiratory diseases like flu, cough, cold, adenovirus infection, influenza virus infection, severe acute respiratory symptoms, COVID-19, and other infections relevant to the respiratory tract.

Gastrointestinal System-related Viral Infection

The viral disease that affects our digestive tract leads to gastroenteritis.

Clinical symptoms of gastrointestinal viral diseases include:

- Abdominal pain/discomfort
- Diarrhea
- Vomiting

Exanthematous Viral Disease

• These viruses cause skin rashes; examples of these viruses are measles, chickenpox, chikungunya, smallpox, and rubella.

Metabolic Viral Diseases

The viral infection that causes inflammation in the liver is called hepatic viral disease. Viral hepatitis can be classified as hepatitis A, B, and C.

Skin Viral Infections

Skin viral infections are generally associated with lesions forming on the skin. In infection cases, lesions disappear for a while and then return.

Hemorrhagic Viral Infections

The viral infection related to the circulatory system is known as hemorrhagic viral disease. Signs and symptoms of hemorrhagic viral infections are bleeding, pain, pyrexia, weakness, *etc.*

Viral Diseases Related to the Nervous System

Examples of these diseases are polio, viral meningitis, and virus encephalitis. The brain and surrounding tissues that are infected can cause symptoms such as pyrexia, confusion, drowsiness, pain, *etc.*

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INDIAN TRADITIONAL DRUGS

It is recognized that traditional systems of medicine have always played a vital role in global health requirements. They are considered as the present as well as the future of the medical system. According to literature, the Indian traditional system has existed since the ancient times, and was known as the Indian System of Medicine. India has a unique diversity, having six recognized systems of medicine *i.e.*, Ayurveda, Siddha, Unani, Yoga, Naturopathy and Homoeopathy. Homoeopathy came to India in the 18th Century. It completely assimilated into the Indian culture and got enriched like any other traditional system; hence, it is considered a part of the Indian System of Medicine [2]. In this chapter, we have

CHAPTER 7

Preclinical Pharmacology of Some Important Indian Medicinal Herbs in Animal Models and Their Mode of Action

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Abstract: Herbs have been used as medicines since the beginning of time and are a rich source of many curative substances. In recent years, there has been a paradigm shift towards medicinal plant research due to the costlier modern drugs available in the market, and potential side effects and resistance developed by many conventional therapeutic agents. Pharmacological screening of medicinal plants using various scientific methods like *in vitro*, *in vivo* as well as *in silico* methods involving different experimental models provides emerging preclinical research exploring their mechanism of action. India is a large repository of many species of medicinal plants. According to a recent WHO estimate, a large amount of plant species, almost 21,000, have the capacity to be used as medicines. Medicinal plants such as *Aloe barbadensis* Mill., *Ocimum tenuiflorum* L., *Curcuma longa* L., *Azadirachta indica* A. Juss, *Piper nigrum* L., *Cinnamomum verum* J. Presl., *Trifolium pratense* L., *Zingiber officinale* Rosc, *Carthamus tinctorius* L., *Piper nigrum, Allium sativum* L and *Andrographis paniculata* (Burm.f.) Nees., *Withania somnifera* L. (Dunal), *Cissus quadrangularis* L., *Plumbago zeylanica* L., *etc.* reported to have therapeutic effects against severe common health ailments. Phytoconstituents present in medicinal herbs like alkaloids, tannins, saponins,

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ferric chloride, phenolics, emodins, and volatile oils showed potential therapeutic activity by interacting with the main targets in cells, such as receptor proteins, biomembranes, or nucleic acid. Biochemical outcomes of experimental studies showed that medicinal plants exert many pharmacological activities. The current review concentrates on the pharmacological activity of some important medicinal plants in various experimental animal models.

Keywords: Experimental animals, Herbs, Preclinical, Pharmacology.

INTRODUCTION

Herbs have been used for medicine since the beginning of time and are a source of many different therapeutic substances. Medicinal plant research is getting much more popular in recent times due to costlier modern drugs available in the market and potential side effects developed by many conventional therapeutic agents.

Pharmacological screening of medicinal plants using various scientific methods like *in vitro* and and *in vivo* studies with simulative studies mainly involves different experimental models providing emerging preclinical research and exploring their mechanism of action. India is a large repository of many species of medicinal plants. Twenty-one thousand plant species have the capacity to be used as medicines, according to the data from WHO [1]. Plants having medicinal values, such as *Aloe barbadensis* Mill., *Ocimum tenuiflorum* L., *Curcuma longa* L., *Azadirachta indica* A. Juss, *etc.* reported to have healing effects against common health ailments. Herbs such as *Piper nigrum* L., *Cinnamomum verum* J. Presl., *Trifolium pratense* L., and Carthamus *tinctorius* L. are used to heal wound sores and boils. *Piper nigrum* L., *Carthamus tinctorius* L., *Santalum album* L., and *Andrographis paniculata* (Burm.f.) Nees demonstrated to have antipyretic activity. Many herbs, such as *Phyllanthus emblica* L., *Tinospora cordifolia* (Thunb.) Miers, and *Azadirachta indica* A. Juss, act as blood purifiers, removing metabolic toxins to change a chronic situation. Studies reported that medicinal herbs, namely, *Allium sativum* L., *Withania somnifera* L. (Dunal), *Achyranthes aspera* L., *Eclipta alba* (L.) Hassk., *Commiphora mukul* (Hook. ex-Stocks) Engl., *etc.*, are effective in reducing hypercholesterolemia. Medicinal plants, namely, *Aloe barbadensis* Mill., *Allium sativum* L., *Allium cepa* L., *Coccinia indica* Wight & Arn., *Cajanus cajan* (L.) Millsp., *Ficus bengalenesis* L., *Ocimum tenuiflorum* L., *Tinospora cordifolia* (Thunb.) Miers., *Swertia chirayita* (Roxb.) Buch.-Ham. Ex C.B. Clarke, *Trigonella foenum graecum* L., *Murraya koeingii* (L.) Spreng., *etc.*, demonstrated to have antidiabetic properties. *Cissus quadrangularis* L., *Plumbago zeylanica* L., *Terminalia bellarica* (Gaertn.) Roxb., *Terminalia chebula* Retz., *Achyranthes aspera* L., *Commiphora mukul* (Hook. ex-Stocks) Engl.**,***etc.*, showed anti-inflammatory action in different animal models [2, 3]. Phytoconstituents present in medicinal herbs like alkaloids, tannins, saponins,

ferric chloride, phenolics, emodins, and volatile oils showed potential therapeutic activity by interacting with the main targets in cells, such as receptor proteins, biomembranes or nucleic acids. These phytochemicals, which are derived from plants, may be able to prevent the development of several chronic illnesses, such as cancer, metabolic disorders, and cardiovascular problems [4]. The present review focuses on the pharmacological activity of some important medicinal herbs in various experimental animal models, which will be helpful for the development of more effective therapeutic agents in the coming years.

PHARMACOLOGICAL ACTIVITY OF MEDICINAL PLANTS

The present review is prepared by collecting information on significant research findings from various sources like Google Scholar, Research Gate, and published articles from journals and books. The review is prepared to document the pharmacological activities of five important medicinal herbs in various experimental animal models and their modes of action.

Aloe barbadensis Mill. (Asphodelaceae)

This important plant commonly known as *Aloe vera* has long been used as a treatment in numerous conventional medical procedures all over the world.

Hepato-protective Activity

Aloe vera aqueous extract, given orally for one week at doses of 250 and 500 mg/kg, significantly decreased the level of aspartate transaminase, alkaline phosphatase and alanine transaminase, which increased due to paracetamol, and significantly restored the liver thiol levels that were depleted in a rat model (albino) [5]. In another animal model, the oral administration of the aqueous extract of Aloe vera leaves at doses of 300 and 500 mg/kg demonstrated a substantial hepatoprotective effect [6]. *Aloe vera* at the oral dose of 500mg/kg showed a highly substantial liver-protective effect in rabbits by decreasing the levels of Serum Glutamic Pyruvate Transaminase, Serum Glutamic Oxaloacetate Transaminase, and direct bilirubin [7]. *Aloe vera* extract administration at the dose of 1mg/ml for 6 days prior to hepato-toxicity induced by carbon tetrachloride in albino rats showed a hepato-protective effect by the restoration of the improved antioxidant enzyme levels, namely catalase, peroxidase, and superoxide dismutase and decreased lipid peroxidation [8]. In streptozotocin-induced diabetic rats, 30% gel of aloe vera (200 mg/kg) therapy decreased the elevated thiobarbituric acid reactive substance (TBARS) while maintaining catalase activity superoxide dismutase at levels consistent with normal. In diabetic rats, gel of aloe vera boosted decreased glutathione by four times [9].

CHAPTER 8

Citrus and its Fight against Cancer

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Abstract: Traditional medicine has made extensive use of natural products, due to their extensive therapeutic applications. There is an increasing demand and acceptance of the use of medicinal plants due to their efficacy. For about 60,000 years ago, plants have been used as drugs according to several works of literature. It is evident that the *Citrus* genus, belonging to the Rutaceae family, possesses a range of pharmacological activities, including anticancer, antidiabetic, antihyperlipidemic, antimicrobial, hepatoprotective activity, and cardiovascular activity. Polysaccharides present in pomelo (*C. maxima*) peels act on S180 (murine sarcoma cells) Tumour-Bearing Mice by improving splenic lymphocyte proliferation ability and inhibiting the activity of NK cells, and leaf extract act on prostate carcinoma DU145 Cells by suppressing constitutive STAT-3 activation. At the same time, alcoholic extract of *Citrus aurantium* bloom showed an appreciable effect against breast cancer and human colon adenocarcinoma cells with IC_{50} 152.34 ± 0.75 µg/mL, 49.74 ± 0.75 µg/mL, and 96.23 ± 0.75 µg/mL respectively. The emulsion prepared from the volatile oil of *C. sinensis* reduced viability in colon cancer cell lines and simultaneously upregulated BAX/BCL-2 along with the suppression of vascular endothelial growth factor. Bergamottin and 5-geranyloxy-7-methoxycoumarin obtained from *Citrus bergamia* downregulated the proliferation of neuroblastoma (SH-SY5Y) cells, inducing apoptosis and positively regulated cell population in the sub-G0/G1 phase. The elevated BAX, downregulated BCL-2, released cytochrome C (cyt. c) in the cytoplasm, and cleaved PARP in breast cancer cells suggest that phytochemical constituents in lemon seed extracts might be a useful source of antioxidants and induce cell death *via* the mitochondrial apoptosis pathway. Bergamottin, a furanocoumarin obtained from peels of *Citrus hystrix* fruits, showed promising activity against pancreatic carcinoma cells by inhibiting survival proteins in the AKT/mTOR pathway. The detailed information on different species of

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the Citrus genus in the field of antineoplastic pharmacology might add value to the scientific evaluation for exploring more medicinal applications of these plants.

Keywords: Apoptosis, Anticancer activity, Citrus, Phytoconstituents, Tumour cell.

INTRODUCTION

Cancer has jeopardized human health by securing the first position in fatality rate on a disease list. This disease weakens not only the patient's health condition but also the financial framework of the victim's family. The rate of survival in this disease state declines due to the commencement of late diagnosis and inadequate treatment facilities. The latter applies to impoverished nations. Cancer cases emerge rapidly because of population expansion and improper human lifestyles like smoking tobacco [1].

Over the years, plants have been a key source of discovering and developing various medicines for human health. Let us not deny the contribution of folklore medicine in treating numerous diseases for centuries across the world. Bioactive compounds derived from plants have established enormous anticancer properties. Dedications and efforts of researchers helped to discover many anticancer drugs such as vincristine, paclitaxel, etoposide, and cisplatin, *etc.*, from several plant sources [2].

Even citrus fruits rich in vitamin c with active phytoconstituents such as flavonoids, hydroxycinnamates, phenols, and terpenes in several species have shown anticancer activities both in preclinical and clinical stages [3]. The unused parts of citrus are generally discarded as waste material. Citrus fruits due to their antioxidant potential, are effective against various malignancies, viz. breast cancer, hepatocarcinoma, and pancreatic cancer, *etc.* [4, 5].

Flavonoids, a group of polyphenolic compounds that are extensively dispersed which can be isolated from citrus fruits, had shown anti-carcinogenic attributes. After many experiments, it was observed that citrus flavonoids or flavanones (naringenin, hesperidin) might be associated with enzyme interactions responsible for cell proliferation and receptor binding [6]. However, few human cancer cell lines were used to exhibit anti-proliferative properties where polymethoxylated flavones inhibited cell proliferation. Likewise, nobiletin, a polymethoxy flavonoid obtained from *Citrus sinensis* and *Citrus reticulata*, pointed out antitumour activity on human gastric cancer cell lines such as TMK-1 and MKN-74, *etc.*, by inducing apoptosis and was determined by various cell cycle assays [7, 8].

Apart from providing a vast application in food, beverages, and cosmeceuticals, essential oils originating from citrus have manifested as antineoplastic agent. Essential oil, namely D-Limonene, promoted apoptosis in the human colon cancer cell line by mitochondrial death pathway and restricting phosphoinositide-3-kinase (PI3K)/AKT pathway [9]. This chapter discusses how the citrus genus can be helpful in cancer prevention.

GEOGRAPHICAL DISTRIBUTION AND TRADITIONAL USES

This genus can be found in tropical and subtropical regions, as well as in Asia, Italy, North and Central America. Although citrus exists in a range of species, the most popular are listed here, along with their traditional applications. Biological source, distribution, and traditional uses of various Citrus species is tabulated in Table **1**.

Table 1. Biological source, distribution, and traditional uses of various Citrus species.

S. No.	Scientific Name	Synonym	Geographical Distribution	Parts used	Traditional Use	Refs.
1	*Citrus maxima*	Pomelo	India, China, Japan, Indonesia, the United States, the Philippines, and Thailand	Leaves, fruits, roots, barks, seeds	Epilepsy, convulsive cough, Hepatoprotective, anti-asthmatic, cough suppressant, anti-epilepsy, cardiotonic and bleeding illness	[10, 11]
2	*Citrus aurantium*	Bitter orange, "*Chih-shi*" or "*Zhi shi*" in traditional Chinese medicine (TCM)	Tropical and subtropical south-east parts	Fruits and peels	Indigestion, diarrhoea, dysentery, constipation, and as an expectorant.	[12, 13]
3	*Citrus bergamia*	Bergamot	Italy	Fruit	Carminative, rubefacient, stimulant, and relaxant, skin disinfection, minor wounds healing, and as medicine against cold.	[14]
4	*Citrus reticulata*	Mandarin	South-East China, India	Peels	Stomach upset, ringworm infections, cough, skin inflammation, and muscle pain, and reducing blood pressure.	[15, 16]
5	*Citrus sinensis*	Sweet orange	Asia	Fruit	Constipation, cramps, diarrhoea, bronchitis, cough, hypertension, and stress	[17]

CHAPTER 9

Andrographolide and its Neuroprotective Potential in Ameliorating Parkinson's Disease

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Abstract: Neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's and Prion-related diseases are age-related progressive disorders. Among neurodegenerative diseases, Parkinson's disease is the second most common disease after Alzheimer's. Every year, millions of people were affected by Parkinson's disease. The formation of α-synuclein protein aggregation associated with degeneration of dopaminergic neurons is the main pathological hallmark of PD. Patients suffering from this disease live in an impairing condition and impose huge financial as well as psychological burdens on society. However, there is no definite treatment till now that can be used to treat Parkinson's disease patients. The current treatment approaches only provide symptomatic relief but can not reverse the disease condition. Hence, there is a need to identify novel, definitive and minimal toxicity-exhibiting treatments for PD. Natural products, specifically medicinal plants, due to their never-matched chemical diversity, always act as a better source for drug discovery. Here, in this chapter, we have selected andrographolide, a plant-derived secondary metabolite of labdane triterpenoid extracted from *Andrographis paniculate,* a traditional herb. Andrographolide shows its neuroprotective potential in PD *via* exhibiting multiple mechanisms like decreasing neuroinflammation induced by microglial activation.

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Activating HSF1 and NRF2-mediated autophagy mechanisms in clearing α-synuclein protein aggregation and regenerating the degenerated dopaminergic neurons, ameliorate the PD symptoms. In this possible way, andrographolide provides a better chance to develop a novel therapeutic tool for treating Parkinson's disease in the near future.

Keywords: Andrographolide, Anti-inflammatory and HSF1 activator, Degeneration of dopaminergic neurons, Parkinson's disease, Neuroinflammation, α-synuclein protein aggregation.

INTRODUCTION

Neurodegenerative diseases (ND) such as Alzheimer's, Parkinson's, Huntington's diseases are progressive disorders that show serious impact on central as well as peripheral nervous systems. In such diseases, part of the brain or the whole brain get damaged due to various factors such as oxidative stress, Endoplasmic reticulum (ER) stress, ischemia, inflammation, viral infection and also the aggregation of non-native proteins [1]. Moreover, symptoms such as behavioral interruption, cognitive impairment and motor dysfunction are associated with neurodegenerative diseases (NDs) and were mainly augmented due to loss of neurons, gliosis, or demyelination [2, 3].

Parkinson's disease (PD) is one of the progressive neurodegenerative disorders, and it is the second most frequently occurring neurodegenerative disorder after Alzheimer's. Parkinson's disease predominately affects people around 60 years. Earlier reports suggest that PD also affects the younger generation between 21 and 40 years of age [4]. Parkinson's disease generally exhibits a series of symptoms such as motor dysfunction associated with static tremors, slow movement as well as uncertainty in balance, gate and posture. In addition to this, Parkinson's disease also exhibits other symptoms such as depression, cognitive impairment, vision impairment, bladder hyperreflexia and disturbance in sleep [5].

Moreover, Parkinson's disease symptoms were mainly associated with the degeneration of dopaminergic neurons, specifically in the substantia nigra region, and increased accumulation of Lewy bodies with α-synuclein protein aggregation, which is the main pathological hallmark of the disease [5]. The actual cause for the degeneration of dopaminergic neurons mostly remains unknown. However, recent evidence suggest that the elevation of neuroinflammatory responses in the brain may be one of the reasons for the development of Parkinson's disease. During this inflammatory response, the microglial cells get activated and release various pro-inflammatory factors, which lead to the degeneration of dopaminergic neurons in the substantia nigra region of the midbrain [6]. Besides, it has also

been reported that faulty sequestration of dopamine into vesicles leads to the production of reactive oxygen species in the cytoplasm, which plays an important role in the degeneration of dopaminergic neurons. In addition to this, there are several other reasons, such as mitochondrial dysfunction, excitotoxicity, trophic factor deficiency, toxic action of nitric oxide, genetic mutations, environmental toxins and apoptosis, which can initiate Parkinson's disease [7].

Parkinson's disease is a destructive neurological condition that affect millions of people every year. Patients with this disease survive in crippling conditions; moreover, it enforces huge financial as well as psychological burdens on the family and also on the society [8]. Till now, there is no specific treatment that can stop Parkinson's disease or that can reverse it. Current treatment approaches such as dopamine agonists, Catechol-o-methyl-transferase (COMT) inhibitors, MAO-B (Monoamine Oxidase Type B) inhibitors and anticholinergic drugs have been suggested to treat Parkinson's disease symptoms. Additionally, Levodopa, a potential drug to treat PD, is associated with severe side effects such as a "wearing off" effect and also causes dyskinesia and other complications in motor functions [7].

Hence, there is an urgent need to identify novel, specific and definite drug treatments for Parkinson's disease. From ancient times, natural products in specific medicinal plants and plant-derived compounds always acted as a promising source for drug discovery for various diseases [9 - 16]. From the recent evidence, it was known that phytocompounds that forcibly activate HSF1 and upregulate its molecular chaperon proteins or heat shock proteins, such as HSP70, 40 and 90, help in clearing the protein aggregates and improve the neurodegenerative disease conditions such as PD [8, 12, 17]. In the same way, the anti-inflammatory compounds obtained from medicinal plants also play a prominent role in neurodegenerative diseases like PD [18].

In this context, andrographolide, a secondary metabolite derived from medicinal plants, was well-studied against various diseases. It is a diterpenoid type of compound and a labdane derivative obtained from *Andrographis paniculata* extract. It possesses a wide range of pharmacological actions such as anti-inflammatory, anticancer, antimalarial, antipyretic, antidiabetic and antiviral effects. Moreover, it has been widely studied for its beneficial effects on neurodegenerative diseases, and it executes neuroprotective potential against various neurodegenerative diseases such as brain ischemia, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and cognitive impairment [18, 19].

From the earlier reports, it was revealed that andrographolide improves the Parkinson's disease condition by regulating the inflammatory response in the

CHAPTER 10

Current Pharmacological Perspectives of Herbal Antidiabetic Drug Formulations

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Abstract: People of all ages are affected by the chronic complications of diabetes mellitus. Numerous synthetic medications have been developed to treat diabetes, which has become more common across the globe. These medications, while effective as antihyperglycemic medicines, come with a number of side effects. They are expensive and out of reach for the vast majority of people who live in underdeveloped nations. Due to their accessibility and harmless nature, medicinal plants have already been traditionally utilized to cure a variety of illnesses throughout history. Phytochemicals found in medicinal plants provide a number of health advantages. Healthcare professionals are looking into plant-based medicines as a potential supply of antidiabetic pharmaceuticals because of their high efficacy and lack of adverse effects as diabetes prevalence rises. The active phytoconstituents are being identified and thoroughly studied in order to gain a better understanding of the mechanism of action of therapeutic plants. Here, we focus on the perspectives of pharmacologically active phytomolecule formulations produced from medicinal plants that demonstrate antidiabetic action and the role they now play in managing and treating diabetes in the present scenario. These natural molecules might be suitable for developing new approaches to treatment or potent treatment options for diabetes.

Keywords: Diabetes, Medicinal Plants, Phytoconstituents, Pharmacology.

INTRODUCTION

The prevalence of Type 2 Diabetes Mellitus (T2DM) is a significant and developing public health issue. Diabetes was predicted to affect 9.3% of the world's population, or 463 million people, in 2019. Now, it is predicted that diabetes will affect 10.2% of the world's population, or 578 million people, in 2030 and 10.9% of the population, or 700 million people, in 2045 [1]. Over 90% of them have type 2 diabetes, which is responsible for over a million fatalities yearly [2]. Lack of insulin, an anabolic hormone, can lead to abnormalities in how

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proteins, lipids, and carbohydrates are metabolized [3]. Low insulin levels, insulin resistance in target tissues, insulin receptor levels, primarily in skeletal muscles and adipose tissue and to a lesser extent in the liver, the signal transduction system, effector enzymes or genes, and/or the signal transduction pathway are the causes of these abnormalities in metabolism [4]. As the disease progresses, tissue or vascular damage causes serious complications, such as diabetic neuropathy, retinopathy, cardiovascular, nephropathy, cerebral, pulmonary, and ulcers, peripheral vascular diseases, and thyroid gland disorders, which have serious morbidity and mortality rates [5]. There are already a variety of anti-diabetic medications on the market to treat hyperglycemia, most of which operate by increasing insulin sensitivity, balancing insulin, increasing insulin secretion, and promoting glucose uptake. Insulin and numerous oral hypoglycemic medications, such as metformin, sulfonylureas, α-glucosidase inhibitors, meglitinide analogs, SGLT-2 inhibitors, thiazolidinediones, DPP-IV inhibitors, and GLP-1 analogs, are being used as available therapy for the treatment and management of diabetes. These medications, which aim to improve insulin sensitivity, enhance insulin secretion, and lower blood glucose levels by boosting glucose uptake or excretion in adipose tissue, are typically accompanied by a variety of negative effects. Some of these include gaining weight, hypoglycemia, digestive system issues, liver damage, kidney failure, hypersensitivity reactions, diarrhea, flatulence, and abdominal bloating [6]. Drug resistance and the fact that there are not enough treatments to stop the disease's long-term effects are two other significant drawbacks of these medications.

The search for alternative medications with higher efficacy, potency, and fewer side effects has been increased due to the problems associated with insulin and oral antidiabetic drugs, as well as the restricted drug tolerance, adverse effects, and expense. It is interesting to note that interest in drug discovery research on natural antidiabetic medicines, particularly those derived from medicinal plants, has grown. These agents may improve β-cell function and treat problems linked with diabetes while having fewer unfavorable side effects [7]. Although no effective treatment for DM has been discovered, it can be managed with insulin, dietary changes, and oral anti-diabetic medications. An alternate treatment option might be provided by herbal medications. The drawbacks of existing anti-diabetic therapy include compromised cost, accessibility, affordability, and tolerance. Herbal remedies have long been used to cure a wide range of ailments because they contain a variety of phytochemicals. They are thought to be naturally effective, safe, and have fewer adverse effects [8]. Due to their availability, cheaper cost, fewer problems, and milder side effects than synthetic medications, herbal medications have been shown to be more effective at controlling and managing diabetes. Herbal remedies work through a variety of techniques to decrease insulin resistance, increase insulin production, protect pancreatic beta

cells, and lower blood sugar levels in the blood [9].

Over the years, thousands of plant species have been utilized as complementary medicines for a variety of illnesses; more than 800 of these have been found to have anti-diabetic properties [10]. These plants have been researched for their ability to cure various forms of diabetes and may serve as sources for future natural antidiabetic drug discovery studies [11]. Several medicinal plants that have historically been employed for their antidiabetic properties are currently being researched for possible commercialization as contemporary medications. In developing nations, where the expense of allopathic therapy is high and the traditional usage of herbs to treat diabetes is widespread, this is especially true [10]. Asian nations like China, India, Sri Lanka, Bangladesh, Pakistan, Nepal, Thailand, Bhutan, and others frequently prescribe traditional herbal treatments [12]. These plants' antidiabetic effects are thought to be mediated through a number of mechanisms, including the stimulation of insulin secretion from pancreatic beta-cells, an increase in insulin binding to receptors, a decrease in insulin resistance, and an improvement in glucose tolerance. Other mechanisms of action include promoting glucose metabolism, enhancing β-cell mass and function, and raising plasma insulin, which lowers blood glucose levels in the circulation [13]. Herbal medicines have historically been used to treat a variety of ailments in addition to diabetes, including ulcers, wounds, inflammation, infections, diarrhea, dysentery, malaria, rheumatism, hypertension, obesity, pneumonia, and kidney problems [14]. The major goal of this review is to examine the traditional plant-based treatments for diabetes and/or their phytoconstituents. These may serve as the foundation for developing novel anti-diabetic medications that are more effective and have fewer side effects than those currently on the market.

MODERN-DAY APPLICATIONS OF ETHNOMEDICINE

Indigenous individuals who care about human health practice ethnomedicine, a traditional form of medicine. It is the source of contemporary medicine as well as all other conventional medicinal systems, such as Ayurveda, Siddha, Unani, and Nature Cure [15]. Through experimentation and blunders, information about plants with therapeutic properties has been passed down from one generation to the next for more than hundreds of years. In the rural and indigenous communities of various developing countries, ethnomedicine is very common [16]. Around 80% of the world's population, according to data gathered from the World Health Organization, relies on traditional treatments [17]. For both conventional and traditional medicines, medicinal plants have long been acknowledged as a significant source of raw ingredients [18]. Since they are readily available to them, natural herbal medicines are the go-to option for India's impoverished and

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Raja Chakraborty

Prof. Chakraborty is currently associated with Assam Don Bosco University, where he serves as both Professor and Principal of the Institute of Pharmacy. Prof. Chakraborty brings over 15 years of experience in teaching and research within PCI-approved pharmacy colleges and universities. He has made significant contributions to the field through the authorship and editing of books, as well as the publication of more than 90 research and review articles in esteemed journals. Additionally, he has served as a co-Principal Investigator on externally funded projects. His professional affiliations include roles as a Life Member, Fellow Member, Scientific Advisor, Editorial Board Member, Advisory Board Member, and Reviewer for various organizations and journals.

Prof. Chakraborty's research focuses on medicinal chemistry, traditional medicine, chemical profiling of phytochemicals, metabolic disorders, and oxidative stress. He has also supervised three PhD scholars. His excellence in teaching was recognized in 2018 with the APJ Abdul Kalam Award for Teaching Excellence by Marina Labs Chennai. He was further honored with a recognition from the Journal of Forestry for the best-cited article of the year. Prof. Chakraborty also completed a notable networking project on Scented Rice from North East India, sponsored by the Department of Biotechnology (DBT) of the Indian government.

Originally from Tripura, India, Prof. Chakraborty completed his foundational education there. His exposure to traditional plant and herbal medicine in Tripura has profoundly influenced his research in natural chemistry, blending traditional knowledge with modern scientific inquiry to advance both health and economic outcomes.

Saikat Sen

Prof. Saikat Sen, M.Pharm, Ph.D., FICS, FBSS, is a Professor and Dean of the Faculty of Pharmaceutical Science at Assam down town University, Guwahati, India. He holds a B.Pharm degree from JSS College of Pharmacy, Ooty, a Master's in Pharmacology from the College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, and a Ph.D. in Pharmaceutical Sciences from Jawaharlal Nehru Technological University, Anantapur, Andhra Pradesh.

Prof. Sen has authored two books, edited three others, and contributed to several peer-reviewed edited volumes published by leading global publishers. His scholarly work includes over 85 research and review articles in prestigious national and international journals. He has presented numerous scientific papers, participated in various national and international conferences, and delivered invited lectures at numerous scientific events.

Affiliated with several professional organizations and journals, Prof. Sen holds roles such as Life Member, Fellow Member, Scientific Advisor, Editorial Board Member, Advisory Board Member, and Reviewer. With over 15 years of experience in teaching and research, he possesses extensive expertise in natural remedies and their therapeutic applications, with a particular focus on herbal medicine.

Prof. Sen's contributions have been recognized with several awards, including the "Prof. APJ Abdul Kalam Award for Young Scientists 2018" from Marina Labs, Chennai, the "Best Faculty Award" from The Science & Technology Awards (STA-18) in 2018, and the "Sushruta Best Young Scientist Award" from the Bose Science Society, Tamilnadu, in 2019. He also received an accolade from the Journal of Forestry Research and, in 2022, was honored with the "Best Teacher in Responding and Executing Task" award at Assam down town University. Under the auspices of the Department of Biotechnology (DBT) of the Indian government, he led a significant networking project on Scented Rice from North East India and continues to supervise the doctoral research of several PhD scholars. Prof. Sen is dedicated to advancing research in traditional and folk medicinal systems and fostering a dynamic research environment.