THE CHEMISTRY INSIDE SPICES & HERBS: RESEARCH AND DEVELOPMENT

VOLUME 3

Editors:
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The Chemistry Inside Spices & Herbs: Research and Development

(Volume 3)

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CONTENTS

PREFACE

VOLUME-3 of the **book series "The Chemistry inside Spices and Herbs: Research and Development**" is an excellent collection of nine chapters having extensive contents related to the detailed exploration of chemistry, pharmacology, and roles of different medicinally treasured plants (herbs and spices) and their constituents. All the chapters have been skilfully written by experts of the field. This book volume covers elaborated reviews on the chemistry and pharmacological properties of different medicinal plants *viz.* plants and herbal products in PCOS (Polycystic ovary syndrome), herbs in the management of rheumatoid arthritis and related inflammatory conditions, Orchid-derived natural flavoring and therapeutic agents' (Vanillin and *Vanilla*) varied pharmaceutical applications, along with their roles in food industry, and fragrance industry, Silymarin in the treatment of hepatic disease, pharmacological properties of *Hygrophila spinosa* along with traditional applications, key diagnostic characteristics, and phytochemical profile, the pharmacological and chemical paradigms of Tulsi (*Ocimum*), chemistry and biological activity of isolated combretastatins from *Combretum caffrum* and current clinical status as anticancer medicines, herbs and spices to treat different cancers, and herbs in the treatment of diabetes.

In **Chapter 1** written by Onder *et al*., with the most recent publications based on *in vitro*, preclinical, and clinical research as a novel viewpoint, a general assessment of the plants and herbal products in PCOS (Polycystic ovary syndrome) has been compiled from the preclinical and clinical point of view. Additionally, based on the ethnopharmacological characteristics of PCOS, traditional uses of the plants have also been assessed. With the hope of conducting herbs and developing new herbal-based products that are beneficial to PCOS, the impacts and underlying mechanisms of herbal medications used as a therapy for PCOS were also discussed.

In **Chapter 2** written by Bharati *et al*., the function of medicinal plants, herbs, dietary supplements, and isolated bioactive compounds from plants in the treatment and management of rheumatoid arthritis is discussed, along with an explanation of how these substances work pharmacologically.

Chapter 3 written by Roy *et al*., highlighted the *Vanilla*'s varied applications in the food industry, fragrance industry, and pharmaceutical sector. This chapter may serve as a medium for interest in additional research into certain bioactive chemicals that will advance technical, scientific, and remedial values.

In **Chapter 4** written by Singh *et al*., the potential of Silymarin in the treatment of hepatic disease has been discussed and explored.

Chapter 5 written by Satpathy *et al*., serves as a handy reference for traditional applications, key diagnostic characteristics, phytochemical profile, and pharmacological qualities of *Hygrophila spinosa*, which will be helpful to future researchers as they explore the plant's phytopharmacology through mechanistic research.

Chapter 6 written by Dobhal *et al*., has explored the pharmacological and chemical paradigms of Tulsi (*Ocimum*) present globally as it has been found to show the activity as antimicrobial, antimalarial, anthelmintic, anti-diarrheal, anti-oxidant, anti-mosquito agents, anti-inflammatory, chemo, and radio-protective, anti-cataract, cardio-protective, anti-hypertensive, anti-diabetic, antiseptic drugs, anti-hyperlipidemic, *etc*. in various studies.

Chapter 7 written by Patel *et al*., aimed to clarify the chemistry and biological activity of isolated combretastatins from *Combretum caffrum* as well as to examine their development, mode of action, research using computer-aided drug design, and current clinical status as anticancer medicines.

Chapter 8 by Agrawal *et al*., is centered on diabetes and accessible diabetic treatments, with a particular emphasis on herbal medicine and clinical trials of these herbal plants.

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CHAPTER 1

Medicinal Plants including Spices for the Treatment of Polycystic Ovary Syndrome (PCOS) with a Preclinical-Clinical Perspective and Phytotherapeutic Approaches

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Abstract: Polycystic ovary syndrome (PCOS) is one of the most common metabolic-endocrine and multi-faceted gynecological disorders for reproductive-aged women. This condition has multiple undesirable effects with psychological, reproductive, and metabolic evidence. Multi-systemic adverse effects and conditions in PCOS cause irregular menstrual cycles, hirsutism, infertility, insulin resistance, diabetes, cardiovascular diseases, anxiety, depression, sexual dysfunctions, and eating disorders. PCOS symptoms are multi-faceted and alterable for each person, leading to different treatment methods evaluated from different perspectives. There are no definitive and ideal treatments for hormonal disorders-related clinical symptoms. Alternative therapies are also considered instead of commercially available drugs. In addition, alternative treatment methods have increased tremendously in recent years due to their minimal side effects. Since the therapies for PCOS require a multidisciplinary approach to understanding all aspects of this condition, medicinal plants should also be considered. The role of medicinal plants, including spices and their bioactive components, has been encouraged to prevent and treat PCOS, with new treatment strategies yielding promising results. Therefore, in this review, a general evaluation of the plants and herbal products in PCOS has been compiled from the preclinical and clinical point of view, with the current publications based on *in vitro,* preclinical, and clinical studies as a new perspective. Moreover, traditional usages of the plants, based on the ethnopharmacological aspects of PCOS, have been evaluated. The effects and underlying mechanisms of herbal medicines used as a remedy for PCOS were also reviewed with the expectation of herbs-spices and new herbal-based products that are effective on PCOS for future treatments.

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Keywords: Clinical, Plant, Preclinical, Polycystic Ovary Syndrome (PCOS), Traditional.

INTRODUCTION

Natural products, including plants and phytochemicals, have desirable benefits for health [1] and are indispensable in treating and preventing diseases, ensuring the continuity of well-being in daily life. While natural products were used in the treatment of observation-based diseases in the past, with the advancement of technology, evidence-based treatment methods started to be used. However, phytotherapy, known as a treatment approach that includes medicinal plants in treating and preventing diseases, is attracting more and more attention than traditional knowledge from the past to the present [2]. Although conventional medicines are the first step in treating diseases, the global use and demand from markets of herbal remedies continue to increase rapidly. In addition, the use of medicinal plants in treating polycystic ovary syndrome (PCOS) have also been raised in this field. PCOS is an endocrine-gynecology disorder frequently emerging, especially in women of childbearing age; its prevalence reaches up to 20% and is accompanied by metabolic changes [3, 4]. Although the enhancement of prevalence is associated with modernization, it is thought that there is an argument that its history dates back to ancient times [5].

There are pharmacological and non-pharmacological treatment approaches for polycystic ovary syndrome, and the use of herbal medicines becomes popular, mainly due to the fewer side effects [6]. Therefore, this review aims to provide information on the definition, diagnosis, and etiology of PCOS. It comprehensively describes the internal and external factors that contribute to polycystic ovary syndrome, besides its history, epidemiology, and clinical findings focusing on its pharmacological and non-pharmacological treatments. Moreover, commonly prescribed drugs are also presented with complete drug information. In this process, several databases, including PubMed, Scopus, Google Scholar, and Science Direct, have been used for the literature survey. Keywords included treatment efficacy, polycystic ovary syndrome, PCOS, treatment, medicinal plants in PCOS, and phytochemicals in PCOS. Consequently, the important plant species are compiled in this chapter with various aspects and the literature approaching ethnopharmacological knowledge including studies of medicinal plants, bioactive components, and phytotherapeutics used for treating PCOS from the past to the present.

HISTORY AND EPIDEMIOLOGY OF POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome, which has characteristic symptoms of polycystic ovary appearance in the ovary accompanied by amenorrhea, infertility, and hirsutism, was first described by Stein and Leventhal in 1935 [7]. Although it is known as "Stein-Leventhal Syndrome" in the literature, as defined in the past [8]. It is also a hormonal disorder for which there is evidence that it dates back to the Paleolithic and Neolithic ages [5]. PCOS was a multi-systemic disease whose diagnosis became more manageable with the rapid development of ultrasonography technology in the 1960s [9].

ETIOLOGY AND PATHOPHYSIOLOGY OF POLYCYSTIC OVARY SYNDROME

The etiology and pathophysiology of polycystic ovary syndrome remain obscured despite modern medical and scientific advances. However, genetic factors, lifestyle, prenatal androgen exposure, and environmental factors play primary role during the emergence of PCOS [10, 11].

The pathophysiological mechanisms (Fig. **1**) are mainly hyperinsulinemia, alterations in gonadotropin-releasing hormone (GnRH), and androgen hormones [12]. Abnormal changes in GnRH secretion increase the luteinizing hormone (LH) secretion in the pituitary gland. For this reason, the ratio between LH and follicle-stimulating hormone (FSH) deteriorates.

Normal or low FSH levels increase the LH/FSH ratio. Thus, androgen release in theca cells (endocrine cells that make ovulation possible) in the stimulated ovary [13], ending with the appearance of hyperandrogenism (Fig. **2**) [14 - 16]. In addition, the increase in the Anti-Müllerian hormone (AMH) may play a role in the formation of PCOS by causing an increase in LH levels by affecting the GnRH level [17].

The role of insulin in the pathophysiology of PCOS has been explained through various mechanisms. In the case of hyperinsulinemia, insulin causes abnormalities in gonadotropin secretion by acting on the hypothalamus. Increased LH induces androgen synthesis in ovarian theca cells [15, 18]. Besides, insulin induces an increase in free testosterone levels by affecting the synthesis of sex hormone-binding globulin (SHBG) protein in the liver [15, 19]. In addition, it increases the activity of cytochrome P450c17α, an important enzyme for synthesizing steroidal hormones, therefore increases androgen levels originating from the ovary and adrenal cortex [20].

CHAPTER 2

Herbs and their Bioactive Compound's Role in the Management of Rheumatoid Arthritis and Related Inflammatory Conditions

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Abstract: Arthritis is the medical term for swelling or inflammation of one or more joints, ligaments, and surrounding tissues. Rheumatoid arthritis (RA) is an inflammatory autoimmune arthritis that is one of the 100 forms of arthritis. Currently, this autoimmune inflammatory arthritis is incurable. Still, treatment is done on an individual basis of symptoms with the primary goal of minimising joint discomfort and inflammation, improving joint performance, and preventing cartilage damage and distortion. Pharmacotherapy of Rheumatoid arthritis includes nonsteroidal anti-inflammatory drugs (paracetamol, naproxen sodium, ketoprofen, diclofenac), biological agents (rituximab, adalimumab, tocilizumab), and disease-modifying anti-rheumatic drugs (penicillamine, sulfasalazine, gold), immunosuppressants (methotrexate, cyclophosphamide), and corticosteroids (prednisolone and methylprednisolone) along with physical therapy. The inability to achieve complete remission from chronic diseases, as well as the expensive cost of new treatments, and the long-term side effects and risks of modern medicine, have all contributed to a rise in public interest in alternative medicine in recent years and different approaches to treating arthritis are continually being researched. Dietary changes, nutritional supplements, and the use of botanicals and phytochemicals are some of the more popular alternative treatment options for RA. Dietary phenolic compounds, terpenoids, saponins, flavonoids, carotenoids, and alkaloids have effectively slowed the progression of arthritic disease because of their ability to alter pro-oxidant and pro-inflammatory pathways. In addition to whole herbs and spices and their extract, many isolated phytoconstituents have been discovered to have healing capability in the treatment of rheumatoid arthritis. These compounds include aconite, brucine, kaempferol, tamaractam, andrographolide, artemisinin, asiaticoside A, bufalin, hecogenin, curcumin, swertiamarin, resveratrol,

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cardamonin celastrol, lapachol, brazilin, thymoquinone, asperosaponin VI, liquiritin, β-elemene, oleanolic acid acetate, ellipticine, hesperidin, and sinomenime. The current review outlines the role of medicinal plants, herbs, dietary supplements, and isolated bioactive compounds from plants in the treatment and management of rheumatoid arthritis, as well as their mechanism of pharmacological action.

Keywords: Anti-inflammatory, Cytokines, Immunomodulator, Phytomolecule, Signaling pathway.

INTRODUCTION

Arthritis is an inflammatory disorder of the joints and connective tissue that causes swelling, pain, stiffness, discomfort, and a reduction in range of motion [1]. Among the hundred types of arthritic diseases, the most common types of arthritis are Osteoarthritis (OA) and Rheumatoid arthritis (RA). Osteoarthritis is also known as degenerative arthritis or wear and tear arthritis since it evolved in reaction to ageing or a certain lifestyle that causes damage to the cartilage [3, 4]. RA is an autoimmune illness in which the immune system targets the body the body's healthy joints and connective tissues, resulting in inflammatory conditions. This condition causes swelling, discomfort, and stiffness in the joints [5]. Rheumatoid arthritis is a chronic condition that can damage several organs in addition to the joints, including the surrounding tissues, eyes, hair follicles, skin, heart, and lungs [6]. If Rheumatoid Arthritis is left untreated for a long period of time, bone erosion and changes in the shape of the joints occur, which cause the feet, hands, or fingers to become malpositioned [7]. Two of the main auto-antibodies used to monitor the diagnosis and treatment of rheumatoid arthritis are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) and play a major role in the pathogenesis of RA [2, 8]. The first line of treatment comprises glucocorticoids (*e.g.*, prednisone, methylprednisolone, Rexona), disease-modifying anti-rheumatic drugs (DMARDs) such as sulfasalazine, methotrexate, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs (*e.g.*, celecoxib, diclofenac, ibuprofen and naproxen), all of which are used to manage pain and inflammation [9 - 11]. Significant therapeutic advancements have been made in recent years for the development of biologicals, particularly for individuals for whom conventional DMARDs and NSAIDs were inadequate or toxic. Nowadays new FDA approved biologics such as Tumour Necrosis Factor (TNF) inhibitors (etanercept, infliximab, adalimumab, golimumab, and certolizumab,), Interleukin inhibitors (tocilizumab and sarilumab), Anti-B-Cell agent (alemtuzumab, rituximab) and JAK inhibitors (tofacitinib, upadacitinib) available for the target specific treatments of RA [12 - 14]. However, many of the side effects are associated with the prolonged use of NSAIDs, DMARDs and newly developed biologicals. Gastrointestinal complications associated with NSAIDs, alopecia, risk of infections, peripheral neuropathy, hepatotoxicity or renal dysfunction are

associated with the use of DMARDs such as hydroxychloroquine and methotrexate [15 - 17]. Anti-TNF medications have been linked to skin cancer, drug-induced lupus, demyelinating neurons, lymphomas, and congestive heart failure. IL-6 inhibitors and JAK inhibitors can result in hyperlipidaemia, increased liver function tests, pancytopenia, inflammatory bowel disease, and pancytopenia [17, 18].

Natural cures have gained popularity as a result of concerns about the safety and expense of contemporary arthritis treatments. A variety of herbal medications have been discovered to be beneficial in treating persistent arthritis [19, 20]. Some plants with anti-rheumatic effects include ginger, thyme, turmeric, cinnamon, garlic, black piper, cayenne, willow bark, boswellia, borage seed oil, ashwagandha, aloe vera, eucalyptus, chamomile, guggul, artemisia, moringa, and asparagus [21].

Herbs can be used as complementary medicine, as an adjuvant with prescription medications for safe and effective therapy, and to lessen the adverse effects of contemporary medicine [22]. Because of their capacity to modify pro-oxidant and pro-inflammatory pathways, phytochemicals such as dietary phenolic substances, phenolics, terpenoids, diterpenoids, saponins, flavonoids, carotenoids, and alkaloids have successfully delayed the course of arthritic illness [23, 24]. Therefore, it is necessary to discover small phytomolecule with good therapeutic effect, lesser side effects and lower cost that can modulate pathogenic immune responses and prevent tissue damage in RA.

NATURAL COMPOUNDS HAVING ANTI-RHEUMATOID ARTHRITIS PROPERTIES

Natural products can prevent arthritis related inflammation in a variety of ways, including immunomodulatory action by regulating the cytokines (IL-6, IL-12, IL-1, TNF-, IL-1, and IL-10) and certain transcription factors such as STAT3 (Signal transducer and activator of transcription 3), IRF-4 (interferon regulatory factor 4), and Foxp3 (forkhead box P3), inhibition of Th17 cells, which induce the synthesis of pro- and inflammatory cytokines and chemokines, and modulation of cross-talk between osteocytes and immune system [25 - 27]. Natural compounds with the aforementioned features might be used as possible therapeutic agents for the treatment of RA, either alone or in conjunction with some standard anti-arthritic medicines. However, their effectiveness and safety in long-term clinical applications must be examined. In this chapter, we go into further depth on a few naturally occurring substances that have been well examined and have undergone clinical testing on both humans and animals to treat rheumatoid arthritis (Figs. **1**, **2** and **3**).

CHAPTER 3

Biochemical, Biosynthetic and Biotechnological Approaches for an Orchid-Derived Natural Flavoring and Therapeutic Agent Vanillin- A Review

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Abstract: Orchidaceae is the highest-evolved family in the plant kingdom and the largest among the monocotyledons. The members of this family are considered not only for their aesthetic beauty but also for their medicinal values. *Vanilla* sp. is one of the members of the family known as the perennial climbing orchid and is a native of Mexico. It is also cultivated in other countries, *viz*. Madagascar, Indonesia, Comoro & Reunion islands, and India (Karnataka, Kerala, Tamilnadu, and Andaman & Nicobar Islands). The major cultivated members of *Vanilla* are *Vanilla planifolia* (Mexican), *V. pompona* (Indian), and *V. tahitensis* (Tahitian). The present study revealed its multiple usages, such as in the food, perfume, and pharmaceutical industries. Vanillin and vanillic acid are the main bioactive components of vanilla flavor, with other (~200-250) components, including *p*-hydroxybenzoic acid, *p*-hydroxybenzaldehyde, *p*-hydroxybenzyl alcohol, anise alcohol, vanillyl alcohol, *etc*. Local communities know its therapeutic value in curing various diseases like fever, spasms, dysmenorrheal, blood clotting, and gastrointestinal distress. Different biosynthetic and biotechnological approaches to this compound were elaborately discussed. This chapter could be a medium to conduct further investigations for specific bioactive compounds that will increase remedial, technical, and scientific knowledge.

Keywords: *Vanilla sp*, Vanillin, Bioactive components, Endophytes, Micropropagation, Secondary metabolites.

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INTRODUCTION

The Orchidaceae is the second largest plant family, just after Asteraceae. This most prominent monocot family contains about 788 genera and approximately 18500 species [1, 2]. They may be terrestrial, growing in the soil, or epiphytic, *i.e*., growing on the trees or on rocks. Water and nutrient-containing swollen stems or pseudo bulbs are common features found in both terrestrial and epiphytic members. The unique features of the family are their floral characteristics, particularly the anther configuration and the structure of pollinarium, which are conventionally used to classify the family [3]. Stamens and ovary joined to form a column-like structure, which are estranged by a beak-like tissue called rostellum. Most of the members of this family are used as ornamental plants, though some plants have other economic importance.

The family Orchidaceae, composed of the monophyletic genus *Vanilla*, comprises about 110 species. Apart from Australia, *Vanilla* species are found throughout the globe. According to Porte`res, 52 species are available in tropical America, 3 in the Pacific area, 31 in Southeast Asia, including New Guinea, 17 from Africa, and 7 in the Indian Ocean Island [2]. The genus *Vanilla* produces several naturally occurring flavoring agents (generally called vanilla), within which vanillin is the most important.

Vanilla is popular worldwide in the food, beverage, perfume, and pharmaceutical industries. It is derived mainly from mature pods of the *Vanilla* spp. specifically *V. planifolia* Jacks. ex Andrews, *V. tahitensis* J.W. Moore, and *V. pompon* Schiede, though the genus consists of approximately 110 species. It originated in Central America, specifically in Mexico as a flavoring agent, and then its production began in Reunion Island in around 1819 [4]. The major constituent of the vanilla flavor is vanillin, a white crystal with a pleasant, sweet, intense fragrance. Chemically, a phenol is replaced with an aldehyde and methoxy group C6–C1 that is less soluble in water at low heat; however, it is readily soluble in organic solvents (specifically ether and alcohol) [5]. The exact profiling of the vanilla flavor and aroma depends on 200 different components, within which vanillin (4-hydroxy- 3-methoxybenzaldehyde) is the prime constituent, which is cured up to 1%–2% w/w from vanilla pods. According to a study in the year 2010, the worldwide sale of vanillin was approximately 15000000 kg per year, and only 1% was achieved by vanilla pods because of the time-consuming and expensive extraction process [6]. Approximately 40,000 vanilla flowers will produce 500 kg of vanilla pods required to extract 1 kg of vanillin [5]. The overall production is about 2000000 kg, which is less than the global demand, thus mainly unable to be fulfilled solely by depending on the plants as the source of vanillin. The bulk production is covered by synthetic means using lignin and eugenol as precursor

ingredients [7]. Artificial resources cannot exactly duplicate the flavor quality of vanilla pod extracts, which is why natural vanilla is costly next to saffron. The quality will significantly vary based on origin, extraction methods, storage conditions, environmental factors, and plant maturity stages [8]. In addition to its uses in the food industry, some reports confirmed its applications as an antioxidant agent, antitumor agent, anti-inflammatory agent, anti-sickling agent, antimicrobial agent, neuroprotective agent and in anti-amyloid aggregation, and inhibition of non-enzymatic glycation, proves the medicinal value of vanillin to cure multiple disorders [9, 10]. In this study, we extracted the maximum available literature on vanillin to enlighten diverse bioactive potencies, which can be used in the future to benefit human civilization as a whole.

BOTANICAL ACCOUNT, LIFECYCLE & GENERAL FEATURES

The Orchidaceae is the largest monocot family, and the monophyletic genus Vanilla is one of its significant members. Different authors claimed variation in the number of species for the genus *Vanilla*. Cameron and Chase claimed the number of species to be 90, Soto-Arenas *et al.* claimed it 107, whereas Govaerts and Porte`res claimed it to be 110 [11 - 13]. However, the International Plant Names Index listed 188 species of *Vanilla* (The International Plant Names Index 2004).

Vanilla planifolia Jacks. ex Andrews is a climber, up to 15 m long; oblong leaves, 12-20× 3-4 cm, acute or acuminate thick; flowers many in racemes, greenish-yellow, up to 5 cm long; sepals and petals hardly oblanceolate; lip slender, trumpet-shaped, smaller than other parts, with short crenulated lobes; capsules long cylindrical, up to 15 cm long, slightly curved, green.

Phylogenetic analyses of the family Orchidaceae were conducted using plastid DNA bar-coding [14]. The Orchidaceae family was classified into five primary monophyletic clades based on the sequence data for the rbcL plastid gene: Apostasioideae, Cypripedioideae, Vanilloideae, Orchidoideae, and Epidendroideae. Cameron *et al.* have conducted additional research on the Vanilloideae subfamily [11, 15 - 20]. Except for the Vanilloideae, now regarded as a distinct subfamily, these clades correspond to the traditionally known sub-families. According to these findings, the *Vanilla* genus was placed in the family Orchidaceae, subfamily Vanilloidae, tribe Vanilleae, and subtribe Vanillinae [16].

DISTRIBUTION AND ENVIRONMENTAL EFFECT

As mentioned in the introduction Mexico is the origin of vanilla and is considered a big presenter to the globe Veracruz of Mexico is the producer of 70% vanilla, and Puebla and Oaxaca states produce the remaining 30%. A negligible amount is

CHAPTER 4

Silymarin: A Boon in the Treatment of Hepatic Diseases

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Abstract: Silymarin is obtained from the seeds of the herb *Silybum marianum* (milk thistle) belonging to the family Carduus marianum. The herb is traditionally used as a liver tonic and in biliary tract disease treatment, dysmenorrhea, and varicose veins. The major bioactive constituents of Silymarin are silychristin, silybin A, silybin B, isosilybin A, and isosilybin B, while other flavonolignans such as neosilyhermin, silyhermin, and silydianin are also present. Due to its cytoprotective anti-inflammatory, and antifibrotic action, it is the most acceptable and safe natural compound in the treatment of hepatic diseases like jaundice, liver cirrhosis, and chronic viral hepatitis. Silymarin functions as a free radical scavenger and modifies the activity of enzymes that cause cellular damage, fibrosis, and cirrhosis to occur. In the present book chapter, the author will explore the potential of the herb in the treatment of hepatic diseases.

Keywords: Disease, Hepatic, Jaundice, Silymarin.

INTRODUCTION

Every year, millions of people lose their lives due to liver cirrhosis [1]. The liver is essential for metabolism, and excretion and plays a significant role in detoxification [2]. The term hepatic is related to the liver and hepatic disorder is a general term that means affecting the normal functioning of the liver [3, 4]. Due to the changing lifestyle, a number of exogenous and endogenous factors and conditions are responsible for the dysfunction of the liver like alcohol abuse, prolonged usage of drugs and chemicals, viral hepatitis, autoimmune hepatitis, and Non-alcoholic fatty liver disease [5], which turn into Cirrhosis over a period of time due to carelessness of early signs of hepatic illness [6]. Despite significant

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developments in contemporary medicine, plant-based medicines have gained the attention of researchers in the treatment of hepatic disorders [7].

As a member of the Carduus marianum family and an ancient medicinal plant, Silybum marianum L. (Milk Thistle) has been employed for ages for the treatment of a wide range of ailments, including gallbladder and liver disorders, protecting the liver from insect stings, snakebites, alcoholism, and poisonous mushrooms [8, 10]. This plant has huge, thorny leaves and a reddish-purple flower. It can be found in North America, Kashmir, Mexico, and Canada [9]. The extract obtained from the seeds or fruits of the plant has an effective therapeutic effect. Since it was believed to be able to remove liver and spleen blockages, milk thistle was first cultivated in Europe and used as a liver tonic to treat jaundice (Nicolas Culpepper, 1616-1654) [10, 11]. Additionally, this plant has been used for generations as a natural remedy for varicose veins, biliary tract, and liver ailments, difficulties with the upper digestive tract, and these issues. Due to its wonderful hepatoprotective results, it is also considered a hepatic elixir [13].

BOTANY

Medicinal species: Silybum marianum L. Gaertn., Cardus marianus L.

Common names: Holy Thistle, Marian Thistle, Mary Thistle, milk Thistle, Our Lady's Thistle, St. Mary Thistle, wild artichoke, Mariendistel, Chardon-Marie.

Family: Compositae/Asteraceae

Plant description: The five to ten-foot-tall, biennial milk thistle has stiff, green, lustrous leaves with prickly edges and white veins that run along their length. The single flower heads are reddish-purple with bracts that have sharp spines at their ends. The portion of the plant used medicinally is the small hard fruits in the blooms known scientifically as achenes, which resemble seeds [12].

Silymarin is a complex mixture of different flavonolignan isomers and polyphenols [14]. The silymarin preparations contain several different flavonoids, like silibinin, isosilibinin, silydianin, and silichristin. Amongst them, the chief bioactive constituent is 'silibinin' (up to 70% of the drug) responsible for the antioxidant effect [16]. Due to the biotransformation of silibinin diastereomers (two diastereomers silybin B and silybin A) into glucuronide derivatives, the antioxidant effect is obtained as a by-product [17]. Silibinin has hepatoprotective and anti-cancer properties, it has undergone considerable *in vivo* and *in vitro* testing. The low levels of bioavailability and solubility of silymarin are the main drawbacks when utilizing it clinically. According to studies, silymarin can prevent the entry and spread of the hepatitis C virus (HCV) by inhibiting the activity of

the microsomal triglyceride transfer protein and the formation of apolipoprotein B [18]. However, as multiple clinical studies show, silymarin does not appear to be able to lower viral concentration *in vivo* [19]. Fig. (**1**) shows the chemical structures of molecules related to silymarin.

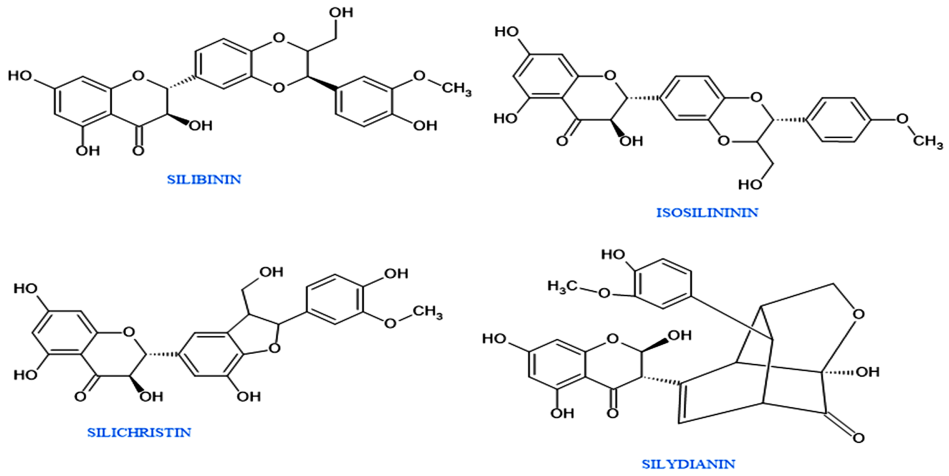

Fig. (1). Molecules of the components of silymarin.

SILYMARIN'S HEPATOPROTECTIVE MECHANISMS OF ACTION

Silymarin's hepatoprotective actions are mediated by several distinct methods, including antioxidant activity and scavenging free radicals, raising cellular glutathione levels, promoting DNA polymerase activity, and stabilizing the hepatic membrane [20, 21]. Fig. (**2**) shows the silymarin's hepatoprotective mode of action.

Antifibrotic Effect

Silymarin also has an antifibrotic impact because it can prevent liver stellate cells from becoming antioxidant enzymes by inhibiting fibrogenic pathways such as those involved in the development of cytoskeletal, electron transfer chains, and profibrogenic collagen [22]. More specifically, silymarin suppresses NF-B, lowers the expression of TGF-ß1 mRNA, and prevents the formation of liver stellate cells [52].

Immunomodulatory Activity

Silymarin's immunomodulatory activity controls the anti-inflammatory response because it inhibits inflammasomes and suppresses NF-B activation, which is crucial for regulating the immune response in inflammatory circumstances [23].

CHAPTER 5

Phytochemistry and Pharmacological Activities of an Ayurvedic medicinal plant, *Hygrophila spinosa*

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Abstract: *Hygrophila spinosa* T. Anders also known as Indian cuckoo is found in moist places and is widely distributed throughout India. Different plant parts are used for disease treatment. The plant contains a variety of secondary metabolites. Furthermore, the plant has pharmacological activities such as antioxidant, antitumor, anti-inflammatory, analgesic, antipyretic, erythropoietic, hepatoprotective, antimicrobial, diuretic, antiosteoporotic, antidiabetic, CNS, androgenic and anabolic, neuroprotective and nephroprotective activities. Here, we have compiled the traditional uses, phytoconstituents, and pharmacological potentials of H. spinosa, which would help researchers in further exploration of the plant.

Keywords: *Hygrophila spinosa*, Pharmacognostic characters, Phytochemistry, Pharmacological potential.

INTRODUCTION

Drugs of natural origin are being utilized in various fields related to health. Different Indian systems of medicine make use of drugs originating from plants. As per the World Health Organization (WHO), around 60-70% of people from developing countries depend on drugs of natural origin for their primary health care [1 - 4]. Plant-based remedies are acceptable due to their easy availability, the least side effects, low prices, and biological effectiveness. The demand and interest in traditional drugs are increasing day by day worldwide [5]. Plants are used in various forms such as crude drugs, extracts, fractions, or isolated active principles for the population of developing countries. WHO is also promoting traditional systems of medicine worldwide for disease treatment [6]. This created

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an awareness and revival of interest in herbal medicines as a system of natural cure.

INTRODUCTION TO THE GENUS HYGROPHILA

The genus Hygrophila belongs to the Acanthaceae family. The plants of this family have, leaves opposite or decussate, simple, estipulate; cystoliths are common on vegetative parts. Flowers are perfect, bisexual, and nearly actinomorphic to zygomorphic. The fruit is typically a 2-valved loculicidal capsule. Seeds 4 (2) - 20, are usually flat, without endosperm; the seed coat is smooth or roughened, often mucilaginous [7 - 9]. Some species of Hygrophila are: *H. salicifolia, H. phlomoides, H. quadrivalvis* Nees, *H. serphyllum* T. Anders, *H. spinosa* T. Anders, *H. obovata, H. ringens, H. polysperma (Roxb.)* T. Anders, *H. difformis, H. erecta, H. megalantha, H. pogonocalyx, H. balsamica, etc* [10].

Hygrophila spinosa (Acanthaceae) is described in Ayurvedic literature Kokilasha or Indian cuckoo is common in moist places and widely distributed throughout India [11 - 13].

Common Names and Vernacular Names of Hygrophila Spinosa

The common names and vernacular names of the plant in various literatures are given below [11, 12, 14 - 22].

Sanskrit: Kakilakshya, Kopilaksha, Atichhatra, Bhikshu, Chhatraka, Ikshugandha, Ikshura, Ikshuvalika, Kakekshu, Kandekshu, Kokilaksha, Kokilanayana, Kolistha, Kshura, Kshuraka, Kulahaka, Pichhila, Pikekshana, Shrigalaghanti, Shrigali, Shrinkhali, Shiklapushpa, Shuraka, Trikshura, Vajra, Vajrakantaka, Vajrasthi, Virataru

Santali: Gokhulajanum

Sinhalese: Katreiriki, Ikkiri

Hindi: Tal-makhana, Talimakhana, Gokhulakanta, Gokshura, Kailaya, Talmakhana-ka-pair, Koleskajhar

Urdu: Talimkhana

Utkal: Kuilirakha, Makheruna, Koillekha, Koilrekha

Konkani: Kolista

Marathi: Talimakhana, Vikhara, Talikhana, Kalsunda, Kolsunda

Bengal: Talimkhana, Kuliakhara, Kantakalika, Kulaka, Shulamardan, Kuliamara, Kulekhade

Malayalam: Nirmalli, Bahelshulli, Vayalchulli, Culli

Tamil: Nirmulli, Neremulli, Nirumalli, Golmidi, Kettu, Nirguvireru, Nerugobbi

Telugu: Neerugubbi, Nirguviveru, Kokilaksamu

Behar: Kantakulika, Talmakhana

Canarese: Kalavankabija

Ewe: Eyitror

Gujerati: Ekharo, Gokhru

Hausa: Dayingiwa, Saregwiwa, Lagargiwa

Punjabi: Talmakhana, Talimkhana

Kannad: Kolavalike, Kolavali, Kolarind, Kolavankal, Kalavankabija

Burma: Soopadan

English: Long-leaved barleria

Assam: Kulekhara

The botanical classification of the plant is:

Kingdom: Plantae-Plants

Subkingdom: Tracheobionta-Vascular plants

Superdivision: Spermatophyta-Seed plants

Division: Magnoliophyta-Flowering plants

Class: Magnoliopsida-Dicotyledons

Subclass: Asteridae

Order: Scrophulariales

Family: Acanthaceae

CHAPTER 6

Diversities of Omnipotent Tulsi: Pharmacological and Chemical Aspects

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Abstract: *Ocimum* is a well-known genus accepted for various ethnopharmacological benefits worldwide. The Tulsi plant is abundant globally; and falls under the Ocimum species. Earlier, numerous species relevant to the Ocimum genus have been identified and cultivated in various parts of the world. Leaves of Ocimum contain 0.1% of essential oils, which are composed of eugenol, citral, ursolic acid, carvacrol, linalool, limatrol, caryophyllene, camphor, and estragole while fatty acids and sitosterol are present in the volatile oil of seed. Eugenol is responsible for its potential effect. The ethnopharmacological aspects of Ocimum species have been reported as antimicrobial, antimalarial, anthelmintic, anti-mosquito agents, anti-diarrheal, anti-oxidant, anti-cataract, anti-inflammatory, chemo, and radioprotective, antiseptic drugs, cardio-protective, anti-diabetic, anti-hyperlipidemic, anti-hypertensive, anti-cancer, pain killer, antiallergenic, antidepressant, memory boosting drugs, antiasthmatic, cough suppressant, diaphoretic, anti-thyroid, anti-fertility, spasmolytic, anti-arthritic, herbal pharmaceuticals, anti-anxiety, and blood thinning activities. In the previous studies, Tulsi has reported the potential effect against cellular toxicity caused by insecticides and industrial chemicals, which is the subject of attention. In this chapter, the author will explore the pharmacological and chemical paradigms of Tulsi that are present globally.

Keywords: Essential oil, Ocimum, Pharmacological effect, Tulsi.

INTRODUCTION

Plants are powerful biochemists and have long been used in phytomedicine; man can obtain a wondrous array of industrial chemicals from them. Antiquity scholastic work included in the Atharvaveda (an Indian religious book), Ayurveda (an Indian traditional system of medicine), and other works provided a rich heritage of knowledge on preventive and curative medicines. Hindus have known India as a nucleus of sacred plants for thousands of years [1, 2]. Clinical manifes-

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tations of these plants are explored in scientific research. Tulsi is considered an extremely holy plant in the Indian culture, not only in terms of goddess Virinda's features but with respect to medicinal factors. It was first mentioned in Rig Veda around 1500 BC. Tulsi become familiar all over the world due to the migration of people [3 - 5]. For many years, it has been reported as a medicinal agent which influences microbial infection, immunity, glucose level, liver function, cardiac activity, dermal infection, insect repellent, anxiety, respiration activity, carcinoma, analgesic, eye disorder, fertility, *etc.* based on *in-vitro* and *in-vivo* studies. The consumable parts of the tulsi plant the seeds, roots, leaves, flowers, and stems either fresh or dried form. Various marketed products are available in the form of capsules, creams, juices, oils, shampoos, infusions, soaps, and tablets [6 - 8]. It is native to India and is also discovered in northern and eastern Africa, Hainan Island, and Taiwan. Cultivation is preferred all over India up to 1800 meters in the Himalayas. Dry, sandy altitude is rich in the tulsi of Hainan and Sichuan of China, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Thailand, and Vietnam. It is flourished in Southeast Asia, Australia, West Africa, and some Arab countries. Tulsi belongs to the Ocimum genus and Lamiaceae family. The Ocimum genus comprises approximately one fifty species including culinary basil and Indian basil or tulsi; it is known as the largest genus of the Lamiaceae family [9 - 11].

Ocimum Sanctum (syn. *Ocimum tenuiflorum*) is grown in two characteristics *i.e.*, green flat large leaves known as Rama, Lakshmi, and Sri tulsi, whereas small purple to blackish leaves known as Shyama and Krishna Tulsi [12, 13]. Other tulsi varieties found in the world are Vana tulsi (*Ocimum Gratissum*), Sweet basil (*Ocimum Basilicum*), Thai basil (*Ocimum Thyrsiflora),* Purple basil (*Ocimum Basilicum),* Lemon basil (*Ocimum Citriodorum),* Vietnamese basil (*Ocimum Cinnamon*), American basil (*Ocimum Americanum*), African blue basil (*Ocimum Kilimandscharicum)*, Italian Genovese basil (*Ocimum Basilicum*), Lemon-scented basil (*Ocimum africanum*), Wild basil(*O. canum), O. minimum, O. suave, O. campechianum, O. adscendens O.micranthum, O.lamifollium, O. urticifolium, and O. ciliatum*, *O.selloi* [14 - 16].

Biochemical Diversities of Tulsi

Numerous tulsi plants exhibit diversities in the morphology and the chemical constituent including secondary metabolite. Although *O. Sanctum* species can be distinguished from others by the yellow color of pollen indicating a high level of eugenol and less chromosome number. *O. Sanctum* tulsi shows 6 times less DNA than *O. Gratissum* [17, 18]. Essential oil extract from the various Ocimum species is known as basil oil, naturally synthesized and accumulated in the peculiar glandular trichomes present in the aerial part of the plant *viz*. leaf, stem, and

flower [19]. Basil oil is extracted through hydro distillation, and supercritical fluid extraction. The content of basil oil differs from 0.5-1.4%. It depends on the species, growing condition, distillation techniques, and geographical region of the plant used. The analysis of basil oil is carried out by the various advanced techniques of GC-MS, and LC-MS [20 - 22]. Amusingly, various Ocimum species have been proven to have diverse chemical profiles, and this diversification of its product has been the focus of numerous research studies aimed at locating commercially important chemotypes. Among the fifty countries of the world, basil oil obtained from Asia tulsi has shown the maximum number of chemotypes; Africa, South America, and Europe comes after that. To date, *O. basilicum* is the most noticed Ocimum species, trailed by *O. gratissimum*, *O. tenuiflorum*, *O. canum*, *O. Americanum,* and *O. kilimandscharicum* [23, 24].

Basil oils are a multi-component mixture of volatile compounds, composed of terpenoids and phenolic compounds. Basil oil is a rich source of secondary metabolites *viz*. monoterpenoids, sesquiterpenoids, phenylpropanoids, ester, and aldehyde [25, 26]. The scent of a tulsi essential oil is due to the presence of 1,8-cineole(eucalyptol), methyl cinnamate, methyl chavicol(estragole), and linalool(coriandrol) in all species of tulsi in the world [27, 28].

Table 1. Secondary metabolites of basil oil in different Ocimum species.

Ocimum Species	Monoterpenoids	Sesquiterpenoids	Phenylpropanoids
O. Basilicum	Camphor (Bornanone), 1,8-Cineole(Eucalyptol), Citral, Geraniol(Rhodinol), Linalool(Coriandrol), Limonene, Linalyl Acetate, Menthone	Bergamotene, Bisabolene, Bicyclo-Esquiphellandren, Cedrene, Cadinol, Farnesene, Muurolol	Anethole (Anise Camphor), Eugenol, Methyl Chavicol (Estragole), Methyl Cinnamate, Methyl Eugenol (Allylveratrol)
O. Gratissum	Bornyl Acetate, 1,8-Cineole, p-Cymene, Rhodinol, Linalool, Ocimene, γ-Terpinene	(Z)-α-Bisabolene, α-Bulnesene, (E, E)-α-Farnesene, α-Humulene	Eugenol, Trans-Methyl Isoeugenol, Thymol
O. Sanctum	1,8-Cineoles, Linalool	Eucalyptol, Linalool β-Bisabolene, β-Caryophyllene, β-Elemene	Eugenol, Allyveratrol
O. Kilimandscharicum	Bornanone, Eucalyptol, Linalool	γ-Cadinene, β-Selinene	Eugenol, Estragole, Allyveratrol
O.Canum	1,8-Cineole, Camphor, p-Cymene(p-Cymol), Limonene, Coriandrol, Terpineol	β-Pinene (Pseudopinene / Nopinene)	Eugenol, Allyveratrol, Estragole, Thymol

CHAPTER 7

Combretum Caffrum Confers a Potential Cutting-Edge Anticancer Molecule as Combretastatins

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Abstract: *Combretum caffrum* (Combretaceae) commonly known as the South African bush willow tree grows naturally along the coast region of the East Cape of South Africa. Combretastatins are emerging chemical molecules discovered from *C. caffrum* tree capable of targeting colchicine binding sites; thus inhibiting the tubulin polymerization for the treatment of cancer. Numerous combretastatin analogues have been found in nature and created artificially, which showed strong cytotoxicity against a variety of cancers, including breast, colorectal, lung, kidney, ovarian, thyroid, liver, leukaemia, pancreatic, and cervical. Combretastatin A-4 was revealed to be the most potent antitumor agent in an isolated extract of *C. caffum*. Combretastatin A-4 is a pioneer in the development of anticancer medicines because of its distinctive features, which include a simple molecular structure, simple synthesis procedure, and anti-tubulin and antivascular activities. The objective of the present chapter is to elucidate the chemistry and biological activity of isolated combretastatins from *C. caffrum*, and to explore the development, mechanism of action, computer-aided drug design studies, and current clinical status as anticancer agents. As orphan drugs, the two Combretastatin A-4 analogs CA-4P and AVE8062 have been approved by the US Food and Drug Administration and the European Medicines Agency to treat anaplastic thyroid cancer (ATC), ovarian cancer, neuroendocrine tumors, gastro-enteropancreatic neuroendocrine tumors, and gliomas.

Keywords: *Combretum caffrum*, Anticancer, Combretastatins, Combretastatin A-4.

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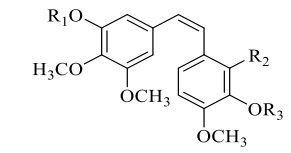
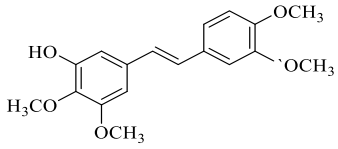
INTRODUCTION

Combretum caffrum (Combretaceae), commonly known as the South African bush willow tree grows naturally along the coast region of the East Cape of South Africa. *C. caffrum* bark was extracted by Pettit and colleagues from Arizona State University in the 1980s and combretastatins were identified as structurally straightforward stilbenoid molecules [1, 2]. A large number of (more than 17) combretastatin analogs have been isolated from *C. caffrum* and are divided into four classes *i.e.,* combretastatins A (CA), combretastatins B (CB), combretastatins C (CC) and combretastatins D (CD) (Fig. **1**) [1 - 4]. The CA are a series of bioactive stilbenes analogs, CB dihydrostilbenes analogs, CC are phenanthrenes analogs and CD series are macrocyclic lactones analogs (Fig. **1**) [4]. All Combretastatins chemically consist of two substituted benzene rings linked by an unsaturated or saturated, or hydroxy-substituted two-carbon bridge maintaining the structural orientation of both phenyl rings tilted at 50−60° with respect to each other [4 - 6]. In CA family, five-membered (CA-1 to CA-5) are *cis*-stilbene derivatives while CA-6 is *trans*-stilbene (CA-6) moiety (Fig. **1**). The CB family (CB-1, CB-2) are dihydrostilbenoids. The combretastatin C family has only one member *i.e.*, CC-1 is a phenanthroquinone compound rarely found as biosynthetic products (4). The CD family CD-1 to CD-4 belongs to a different type of macrocyclic lactone compounds isolated from both *C. caffrum* and *G. floribunda* [7 - 9].

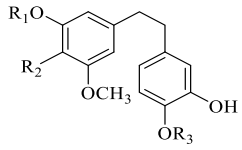
Combretastatins bind to the colchicine site of tubulin and strongly inhibit the tubulin polymerization by binding to the colchicine site [5, 6]. Microtubules play essential roles in various cellular functions, including cellular division, motility, intracellular transport, and maintenance of cellular shape. Microtubule assembly can be interfered either by inhibiting tubulin polymerization or by inhibiting microtubule disassembly to cause orthophase arrest. Therefore, the inhibition of microtubule function using tubulin targeting agents is proven to be an effective method of treating cancer [10 - 12]. Molecular targets such as microtubules have been identified as fascinating and well-established targets for anticancer therapy, as microtubule polymerization dynamics have a major influence on crucial processes, like mitosis and cell signaling [13 - 19]. Many of the tubulin targeting agents currently used in clinical practice, such as taxol, vincristine, and vinblastine, possess complex molecular structures. In contrast, combretastatin has a relatively simple molecular structure, making it easier to design and synthesize. This advantageous feature has led to the development of numerous analogs of combretastatin, which have been designed, synthesized, and evaluated for their potential anticancer activity.



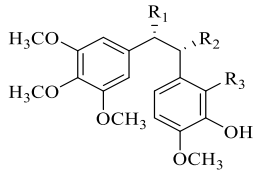
R_1	R_2	R_3	
CH_3	OH	H	Combretastatin A-1
H	H	H	Combretastatin A-2
CH_3	H	H	Combretastatin A-4
H	H	CH_3	Combretastatin A-5



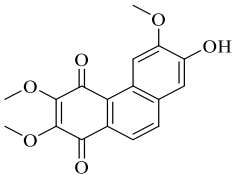
Combretastatin A-6



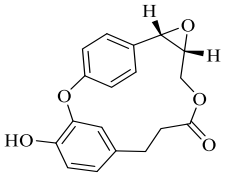
R_1	R_2	R_3	
H	OCH_3	CH_3	Combretastatin B-2
CH_3	OCH_3	H	Combretastatin B-3
CH_3	H	H	Combretastatin B-4



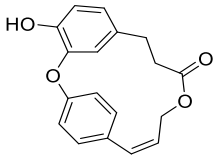
R_1	R_2	R_3	
OH	H	H	Combretastatin 7
H	OH	H	Isocombretastatin A
		OH	Combretastatin B-1



Combretastatin C-1



Combretastatin D-1



Combretastatin D-2

Fig. (1). Structure of selected members of Combretastatin family.

BIOLOGICAL ACTIVITY OF COMBRETASTATIN

Combretastatin and its analogs have demonstrated antibacterial, anticancer, anti-inflammatory, antioxidant, antimicrobial, and antiviral activities. Throughout history, various species of Combretum have been traditionally employed for their medicinal properties. These plants have been associated with the treatment of several ailments, including syphilis, conjunctivitis, diarrhea, toothaches, peptic ulcers, and dysentery [20, 21]. The isolated compound CB-5 revealed bactericidal effects against *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Enterococcus faecalis* [21]. Combretastatin A-4 (CA-4) exhibited moderate antifungal activity against the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes* [22]. Combretastatins and hetero combretastatin

CHAPTER 8

The Role of Herbs in the Treatment of Diabetes

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Abstract: Diabetes mellitus is a chronic metabolic disorder whose prevalence has been steadily expanding worldwide. Diabetes can cause complications with time, which include failure of the heart and the kidney, and a reduction in the quality of life. Continuous administration of allopathic drugs such as biguanides, sulfonylurea (Hypoglycaemic agents), and insulin causes many side effects such as Hypoglycaemia, stomach upset, *etc.*, and have a high cost due to which researchers take eager interest in studies on herbs to find novel chemical compounds for the treatment of diabetes. Some diabetologists have recently found evidence that a therapeutic supplement containing plant derivatives is required to optimise diabetes treatment. Herbal medicine research has grown in importance in recent decades, and the usage of natural products in the cure of diabetes is becoming more popular around the world. They have the property to act as an antibacterial, antifungal, antidiabetic, and anticancer. Herbs are used nowadays, in place of high-cost prescribed drugs. There are many medicinal plants or herbs that are used in the treatment of diabetes such as *Allium sativum*, *Trigonellafoenum graecum* (Fenugreek), *Cuminum cyminum* L (Cumin), *Cinnamomum verum* (Cinnamon), *Ocimum sanctum* (Holy basil), and *Tinospora cordifolia* (Guduchi). Diabetes is caused mostly by oxidative stress and a rise in reactive oxygen species, which can have serious consequences. Many herbs include natural antioxidants, including flavonoids, C and E vitamins and tannins, which hold the capacity to lower blood glucose levels. Medicinal plants help to improve fasting blood sugar levels and, function of the kidney. This study focused on diabetes and accessible diabetic treatments, with a particular emphasis on herbal medicines and clinical trials of these herbal plants.

Keywords: Diabetes, Glucose level, Herbal, Herbs, Medicinal plants.

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INTRODUCTION

Diabetes mellitus is a metabolic illness that can be inherited or have environmental origins. Patients suffering from diabetes mellitus have an amplified hazard of developing a number of ailments. There are presently no effective medications to treat this ailment, and the available therapies are successful for some people but not for all. Therefore, there is a great demand for innovative anti-diabetic drugs [1].

Novel anti-diabetic drugs are, therefore, greatly needed. On the other side, obesity is a serious public health issue that may trigger the emergence of several other medical issues, including type-2 diabetes (T2DM). Because homeopathic and allopathic treatments for this condition are only partially effective, new substitute approaches should be created with long-term efficacy and minimum side effects in mind. Herbal compounds have a higher level of intrinsic structural variation than synthetic molecules. They have so far established themselves as a crucial cause of bioactive compounds and have greatly aided in the identification of new drug research leads [2].

Early detection, treatment, and dietary modifications are necessary for diabetes. The fifth biggest cause of death in the twenty-first century is diabetes, a condition that affects a lot of individuals [3].

Diabetes complications, which are common, have a diverse aetiology, a progressive course, and an urgent need for efficient therapies. Diabetes can now be managed with a variety of therapies, including insulin therapy, medication, and nutrition therapy. To treat diabetes, numerous glucose-lowering drugs employ a variety of mechanisms. These methods involve delaying the carbohydrate's absorption from the gut by alpha-glucosidase, boosting peripheral glucose absorption by thiazolidinediones and biguanides, and stimulating the secretion of insulin by sulfonylurea and meglitinides medicines [4, 5].

Despite the considerable advancements in diabetes therapy over the past three decades, patient outcomes are still far from ideal. These treatments have some drawbacks, such as toxicity, side effects, and medication resistance (decrease in effectiveness). For instance, 44% of patients have a loss of sulfonylurea efficacy after 6 years of therapy. Additionally, it is claimed that hyperlipidaemia cannot be controlled by glucose-lowering medications [6].

The adverse effects of medications and how they interact with one another *in vitro* must also be considered by health workers. Numerous treatments utilising medicinal plants are advised. Many plants have anti-diabetic properties and contain alkaloids, flavonoids, carotenoids, terpenoids, and glycosides [7].

The anti-hyperglycaemic benefits of plant therapy are frequently a result of their capacity to enhance the function of pancreatic tissue, which is accomplished by raising insulin releases or lowering intestinal absorption of glucose. Today, there is a rising number of diabetics, which is raising concerns among the public and the medical profession. The researcher's main goal is to provide a diversity of useful plants having medicinal value for the treatment of diabetes as well as additional plant chemicals' physiological mechanisms for lowering blood sugar and boosting insulin production [8, 9].

Numerous diabetic patients are interested in complementary or alternative therapies that include herbal medications. The potential of having good glycaemic control or being less dependent on insulin injections by taking herbal remedies is undeniably alluring because several popular herbs are said to lower blood glucose levels [10]. The choice of herbs, however, may be influenced by a number of variables, including the stage at which the patient's diabetes is progressing, the types of comorbidities they are experiencing, their accessibility and cost, as well as their safety profile. Preclinical research has extended beyond the walls of labs and is now at the bedside of patients [11].

Herbal products can be used for more than just nutritional purposes like food and nourishment; they can also be used as a treatment for a number of disorders [12]. The use of various plant components, including fruits, leaves, flowers, roots, berries and bark for therapeutic purposes is known as herbal medicine, often denoted as phytomedicine or botanical medicine [13, 14].

Today, therapeutic plants are still used, and it has been calculated that about one-fourth of all prescription medications in the world come through plants. Additionally, according to the World Health Organization, traditional medicine is used for most countries' primary healthcare requirements [15].

MEDICINAL HERBS

The existence of therapeutically significant phytochemicals in the following medicinal plants gives them huge potential in the treatment of many diseases. All the plants included in this review are indigenous to Asian nations and are frequently utilised by traditional healers to treat diabetes [16].

Traditional medicine is heavily utilised in healthcare delivery systems in different portions of the world. In fact, 40-45% of the global population believes directly or indirectly in conventional medical systems, with 80% of those in undeveloped countries relying almost exclusively on traditional medical practises, particularly herbal medicines [17].

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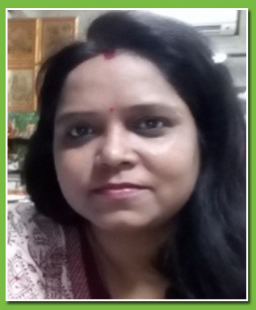

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