MEDICINAL PLANTS: SECONDARY METABOLITIES, UTILIZATION, HUMAN HEALTH-I

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 Institution of Economic Development and Social Researches Publications®
(The Licence Number of Publicator: 2014/31220)
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USA: +1 631 685 0 853
E mail: iksadyayinevi@gmail.com
www.iksadyayinevi.com

ISBN: 978-625-367-599-8
Cover Design: Eda KOÇAK
December / 2023
Ankara / Türkiye
Size= 16x24 cm

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PREFACE

Medicinal and aromatic plants; They are plants that have many uses such as food, medicine, cosmetics and spices, and have been used for similar purposes since the beginning of human history. Hippocrates, also known as the "father of medicine", said, "Make food your medicine, and your medicine your food."

While some of the plants in question are collected from nature, some are cultivated and produced. However, a significant part of the plants used for therapeutic purposes are collected from nature. The most striking and researched features of medicinal and aromatic plants are their use for therapeutic purposes. Treatment with plants is used in many countries of the world, especially in underdeveloped countries, under different names such as traditional treatment, complementary treatment, natural treatment. In parallel with the consumption of medicinal and aromatic plants in many different areas and branches of industry, the world trade volume of these plants is increasing day by day. With the growth of trade volume and increasing demand, efforts to increase the production opportunities of medicinal plants are also accelerating.

This book, which deals with medicinal and aromatic plants from different aspects and was prepared with the participation of valuable scientist, consists of 14 chapters. I would like to thank all our authors who contributed to the preparation of this book titled 'MEDICINAL PLANTS: SECONDARY METABOLITIES, UTILIZATION, HUMAN HEALTH-I', and the employees of IKSAD publishing house who contributed to the publication phase, and I hope that this book will be useful to the scientific community.

Best regards

Assoc. Prof. Dr. Gülen ÖZYAZICI

Assoc. Prof. Dr. Esra UÇAR

CHAPTER 1

EFFECTS OF MEDICINAL PLANTS CONTAINING POLYPHENOLS ON INFLAMMATION AND OXIDATIVE STRESS

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DOI: https://dx.doi.org/10.5281/zenodo.10454492

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INTRODUCTION

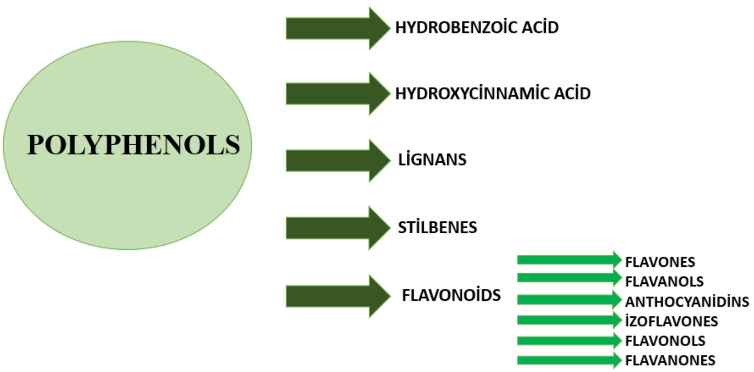
It is well recognized that there is an imbalance between the production of reactive oxygen species, which produce oxidative stress, and the removal of these species by defensive systems, which may result in inflammation. This imbalance results from oxidative stress activating various transcription factors and changes in the expression of some genes responsible for inflammation. Oxidative stress-induced inflammation is directly related to various chronic diseases. Polyphenol-containing compounds are frequently used for therapeutic purposes because they constitute an adjuvant treatment by inhibiting the enzymes involved in the formation of eicosanoids and their antioxidant activities. Compounds including flavonoids, proanthocyanidins and phenolic acids are widely found in plants as a defense mechanism against abiotic and biotic responses. Herbs, spices, vegetables, fruits and grains are common polyphenol-containing foods, and high doses of them are associated with a reduced risk of chronic, neurodegenerative diseases caused by oxidative stress and inflammation. Polyphenols are compounds that contain more than one phenol group in their structure. Compounds called flavonoids are modified or polymerized derivatives of these molecules with tannins and phenolic acids. It is classified as polyphenols, flavanols, flavanones, flavonols and hydroxycinnamic acids. Although the antioxidant properties of polyphenols are accepted, it is known that their bioavailability and effects in the body vary depending on the molecular target. (Serafini et al., 1994). It is also known that polyphenols have a protective effect on many chronic diseases, including type 2 diabetes and cardiovascular diseases. (Jumar & Schmieder, 2016; Martin et al., 2016; Pang et al., 2016; Santos & Lima, 2016; Yang et al., 2014). Polyphenols are chemical compounds naturally found in vegetables, fruits and grains. Plants produce polyphenols as secondary metabolic byproducts. Polyphenols are a complex class of more than 10,000 compounds with one or more aromatic molecular structures connected by one or more hydroxyl (OH) groups. In general, plants produce polyphenols to shield themselves from harmful environmental agents like UV radiation, fungus and animals. Furthermore, polyphenols are essential for the development of plant organoleptic qualities, particularly in the preparation of food and cosmetics. (Pandey & Rizvi, 2009). Tea, a beverage derived from the *Camellia sinensis* plant, is the main source of flavonoids (or polyphenols) in the diet. Tea and the components found in its structure prevent the formation of tumors in different organs, including mammary glands, lung, esophagus, liver, oral cavity, stomach, small intestine, skin, prostate, colon, pancreas and bladder. Administration of black tea, green tea, epigallocatechin-3-gallate or theaflavins during the initial or progression stages has been shown to significantly inhibit tumor tissue formation in (4-methylnitro-samino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung cancers. has been shown to reduce (Yang et al., 2002;. Yang et al., 2005). When administered topically, tea polyphenols and caffeine inhibit the development of skin cancer. However, the decreased skin absorption of tea polyphenols when taken orally can reduce their inhibitory impact and help to prevent cancer from developing (Lu et al., 2007). It was shown that in a mouse prostate model, oral infusion of green tea polyphenols greatly reduced the incidence of prostate tumors and their metastasis (TRAMP). A reduction in insulin-like growth factor levels (IGF)-1 is linked to this inhibitory action. (Khan et al., 2006).

Diferuloylmethane (Curcumin) is a type of polyphenol obtained from the East Indian plant Curcuma longa, also known as turmeric. It has no toxic effect. It is widely used because it has antioxidant, anti-inflammatory, analgesic and antiseptic activity properties. Curcumin has recently been found to have anti-cancer activities in various pathways such as oncogene expression, mutagenesis, cell cycle regulation, apoptosis, metastasis and tumorigenesis. Curcumin has been studied in many human carcinomas, including colon, melanoma, pancreatic, head, neck, breast, prostate, and ovarian cancers (Aggarwal, 2008; Elattar & Virji, 2000; Hanif et al., 1997; Lin et al., 2007; LoTempio et al., 2005; Siwak et al., 2005) and its inhibitory effect on carcinogenesis has been demonstrated with experimental models (Collett, 2001; Inano, 1999; Krishnaswamy et al., 1998).

Numerous studies have demonstrated the anti-inflammatory and antioxidant properties of polyphenolic substances, with a focus on their ability to protect against chronic illnesses and metabolic disorders (Ganesan & Xu, 2017). It is believed that the effect of polyphenols on antioxidant mechanisms is mainly responsible for their disease-protective potential. Additionally, polyphenols function as bioactive agents that suppress inflammation and new vessel formation (Compaore et al., 2018; Ding et al., 2020). To prevent diseases, one must maintain a healthy diet and lifestyle. Flavonoids, in particular, have been extensively researched in recent years, to reduce risk factors in chronic diseases and to be used as antioxidant agents against diseases, as they are abundantly found in plant-based dishes and excipients such as vegetables, fruits, and beverages (Stockley et al., 2012). Many of the flavonoids are conjugated to acids, sugars and alcohols, and all of these phenolic compounds show biological activities. The Mediterranean diet (foods rich in polyphenols) has been reported to be associated with positive health outcomes in the elderly, such as improving mental processes and minimizing the risk of cardiovascular disease (Teng & Chen, 2019).

1. CLASSIFICATION AND STRUCTURE OF POLYPHENOLS

Phenylalanine, along with its precursors, are plant phenolic intermediates that are generated by a natural biosynthetic route that also produces shikimic acid. Polyphenols primarily contain residues of sugar linked to the OH group, even though carbohydrates (mono-, dis-, and polysaccharides) bond directly to the aromatic carbon. Other chemicals conjugated to the phenolic structure are; natural acids, amines, carboxyl groups, lipids and other phenolic groups (Spencer et al., 2008). These substances are generated via the phenylpropanoid and shikimate pathways and are referred to as secondary metabolites (Han et al., 2007). Generally, polyphenols are divided into several groups based on their structure and amount as a component of the phenolic ring. The molecular size, degree of polymerization, conjugation with other phenolic compounds, glycosylation, acetylation, and hydroxylation of dietary polyphenols, as well as their structural arrangement, all have a significant role in their absorption and bioavailability. The diverse sugar moieties that glycosylate polyphenols in their structural components have an immediate impact on their biological activity. Plants contain glycosized flavonoids in the form of C- or O-glycosides. Various biological properties such as antidiabetic, antibacterial, anti-inflammatory, anticancer, antioxidant, antifungal and anticoagulant are enhanced by O-glycosylation. The four primary classes of polyphenols are lignans, phenolic acids, stilbenes and flavonoids (Pandey & Rizvi, 2009).



1.1. Phenolic Acids

Cinnamic acid and benzoic acid are the two categories of phenolic acids that are frequently present in food. (Pandey & Rizvi, 2009). These compounds, derived from hydroxybenzoic acid, have a carboxylic (COOH) group in their structure. Hydroxycinnamic acid derivatives have a three-carbon chain attached to the benzene ring containing at least one hydrogen atom that can be replaced by a hydroxy (-OH) group (Iglesias-Carres et al., 2019). Plants have minimal levels of hydroxybenzoic acid, except for some types of black radishes, onions and red berries (Tungmunnithum et al., 2018).

1.2. Flavonoids

Flavonoids are polyphenol derivatives containing 2 aromatic rings (Flanagan et al., 2018; Huyut et al., 2017). Flavonoids; are classified as flavones, isoflavones, anthocyanins, flavanols, flavanols and flavanones (Panche et al., 2016). It is believed that consuming foods high in flavonoids over an extended period may improve human health and lifespan (Bondonno et al., 2019). Anthocyanins, which suppress cyclooxygenases (COX1 and COX2), improve endothelial function and exhibit antiatherogenic, antihypertensive, antiglycation, antithrombotic and anti-inflammatory properties. Furthermore, flavonoids are crucial for processes including lowering oxidative stress, enhancing cognition and memory, and diminishing neuroinflammation (Devi et al., 2021).

1.3. Stilbenes

In many other plant species, like peanuts, Stilts, sorghumes and gymnosperms, benes are phenylpropanoids (Parage et al., 2012). It consists of 2-phenyl moieties connected by a methylene bridge. The concentration of stilbenes taken with the diet is very low. The main reason for this is that stilbenes function primarily as antimicrobial phytoalexins in plants and are produced in response to injury or infection. 3,4′,5-trihydroxystilbene, known as resveratrol, is a natural stilbene found predominantly in grapes and their derivatives (Basholli-Salihu et al., 2016; Wang et al., 2012). Stilbenes have been the subject of numerous research, and the results indicate that they may be helpful in the management of hepatic illnesses, cardiovascular disorders, diabetes, obesity, pain, inflammation, cancer and neurodegeneration (Yeung et al., 2019).

1.4. Lignans

Unlike the racemic polymer lignins that form the backbone of plant cytomembranes, lignans are a polyphenol derivative and are resinous, non-caloric plant substances (Bagniewska-Zadworna et al., 2014). Lignans, a phenolic compound, are formed by the dimerization of 2 cinnamic acids (Garros et al., 2018). The bioavailability of polyphenols found in diets in malignancy phenotypes is dependent on the capability of lignans to influence cellular processes (De Silva & Alcorn, 2019; Mocanu et al., 2015).

2. BIOAPPROACH OF POLYPHENOLIC COMPOUNDS

Polyphenols show biological properties in plants such as protection from UV rays and a variety of environmental factors (Bakoyiannis et al., 2019) and produce metabolites that are primarily responsible for nutritional effects (Wojtunik-Kulesza et al., 2020). Many factors, including molecular size, conjugation with other substances, polymerization, food quality, matrix release, and solubility levels, influence the amount of polyphenols (Teng & Chen, 2019). These phenolic compounds are poorly absorbed in the small intestine, with 5-10% of their gross weight being transferred into the circulation. Phenolic compounds, which are only deglycosylated in their natural form, undergo glucuronidation, sulfonation and methylation in the liver after absorption, making it easier for phenolic compounds to enter the bloodstream. Phenolic compounds, which cannot be absorbed in the small intestine due to their complex structure, are converted into small molecular structures and become biologically useful (Sobhani et al., 2021).

Chronic disorders, which include many neurological conditions and metabolic syndromes, are mostly caused by inflammation. The inflammatory response is an important defense system for infections that develop due to microbial invasion or injury, and this condition, which causes tissue damage, is associated with the disruption of immune homeostasis. Examining the effect of dietary polyphenols in the regulation of this homeostasis mechanism is very important in preventing inflammatory diseases. The inflammation-suppressing capacity of dietary polyphenols is due to their functions such as acting as antioxidants, suppressing pro-inflammatory signals and interfering with oxidative stress signals. The agonistic activation of cellular pathways of signalling by polyphenol chemicals makes them physiologically significant in addition to their direct reaction with reactive oxygen species (Dandona et al., 2005; Scalbert et al., 2005).

2.1. Antioxidant Activity

Exposure to noxious stimuli such as chemical and mechanical stress, physical injury, redox imbalance, metabolic disorder, and oxygen and glucose deprivation contribute to the impairment of immune regulatory functions in autoimmune diseases. These stimuli cause systemic or localized or acute or chronic inflammation, and acute inflammation causes the release of cellular mediators such as prostaglandins, cytokines and ROS, which are produced to protect tissues and cells. Nitric oxides (NO^-), superoxide anions ($O2^-$.) and hydroxy radicals (OH^-) are important for human health due to their roles in preventing pathogen invasion, respiratory burst in neutrophils, and wound healing. In addition, the long-term immune response may also cause tissue damage caused by dysregulation of the immune mechanism. Exposure to various stimuli such as drugs, xenobiotics, heavy metals, pollutants, radiation, and cigarette smoke contributes to the production of ROS species, which are the primary cause of oxidative stress (Reuter et al., 2010).

Phenolic compounds taken with diet are powerful antioxidants. Free radicals can be neutralized by donating a hydrogen or electron atom to various reactive oxygen, chlorine species and nitrogens. In addition, phenolic compounds interrupt lipid autoxidation as an effective radical scavenger and act as chelators to convert metal pro-oxidants and hydroperoxides (Tsao Rong & Li HongYan, 2012). Phenolics inhibit the step propagation of lipid autoxidation chain reactions as effective radical scavengers, or act as metal catalysts to convert hydroperoxide and metal prooxidant into stable compounds. As a chelating agent, phenolic compounds directly inhibit Fe^{+3} reduction. Thus, it reduces the production of reactive OH^- produced by Fenton reactions (Perron & Brumaghim, 2009). Phenolic acids and flavonoids are both compounds with radical scavenging activity, but their metal chelating and inhibition ability varies depending on their structural properties.

The antioxidant activity of phenolic compounds may vary depending on proton transfer, single electron transfer, and hydrogen atom transfer (Tsao Rong & Li HongYan, 2012). In addition, the antioxidant activity of a phenolic compound varies depending on the position and number of OH groups in the molecule. For example, quercetin, a flavanol type containing a 3-hydroxy group, shows relatively high antioxidant activity (Tsao, 2010). Additionally, flavonoids show higher antioxidant activity as the number of aromatics containing hydroxyl groups increases (Van Acker et al., 1996).

Although phenolic compounds are powerful antioxidants when they lose an electron, it should be noted that the molecule itself becomes a relatively stable radical form, and its oxidized intermediate products can also turn into pro-oxidants. The interaction between transition metal ions and polyphenol compounds results in the formation of these pro-oxidants. Oxidation products such as semiquinones and quinones can form pro-oxidants (Halliwell, 2012). In humans, the gastrointestinal tract is the place where these pro-oxidants are formed as a result of the formation of high amounts of metal ions due to excessive intake of polyphenol-containing substances (Barbehenn et al., 2005). For this reason, the use of foods containing polyphenols creates a strong response against oxidative stress, while consumption in high doses may cause pro-oxidant formation (Bouayed & Bohn, 2010).

Determination of antioxidant activity in polyphenol-containing compounds generally occurs in phenol extracts and chemical models. In addition, many antioxidant analysis methods such as oxygen radical absorbance capacity, photo chemiluminescence, ferric reducing antioxidant power, and 2,2-diphenyl-1-picrylhydrazyl have also been developed (Tsao Rong & Li HongYan, 2012).

Polyphenols and their metabolites have low concentrations in the majority of chemical-based assays because of their limited bioavailability. Cell-based antioxidant analyzes are closer to physiological conditions and provide better results in measuring the activities and concentrations of phenolic compounds and antioxidants (Wolfe & Liu, 2007).

The rapid metabolism and low solubility of phenolic compounds cause low bioavailability in in vivo studies. Furthermore, it is challenging to confirm in vivo the systemic impacts of inadequately absorbed phenolic substances due to complex antioxidant systems. Polyphenols taken with the diet are primarily depolymerized in the colon and gastrointestinal tract. Then, organic phenolics and the microbial products of these substances are metabolized in the liver as phase 1-2 and are absorbed into the circulation and transported to the tissues. It is excreted in the urine after undergoing glucuronidation, sulfation and methylation in organs and tissues (van Duynhoven et al., 2011). The antioxidant activities of these compounds normally decrease due to inhibition resulting from conformational differentiation of phenolic OH groups (Procházková et al., 2011).

2.2. Anti-Oxidative Stress Activities

Depletion of substances with antioxidant capacity or accumulation of ROS species alters the redox balance and thus causes oxidative stress. A complex cellular redox system consisting of glutathione reductase (GR), peroxiredoxins (PRX), catalase (CAT), glutathione peroxidase (GPX) and superoxide dismutase (SOD) is a mechanism that protects the cell against oxidative stress (Bhattacharyya et al., 2014). However, this mechanism is inadequate in the presence of excessive ROS (Pham-Huy et al., 2008). Phenolic compounds produce a defense mechanism by plant cells in the presence of stress stimuli such as microbial infection (Howitz & Sinclair, 2008). The protective effect of phenolic compounds is achieved by consuming foods containing these compounds. It is known that consumption of these polyphenols ensures redox homeostasis and prevents localized inflammation by increasing the activity of SOD, CAT, GPX, GR. The expression of these detoxifying enzymes is modulated by erythroid-related factor (Nrf)-2. Nrf2 regulates transcription through antioxidant-responsive elements (ARE) of several genes encoding antioxidant enzymes. Polyphenols induce Nrf2 activation to increase the expression of cellular antioxidant enzymes (Kansanen et al., 2013). In addition, polyphenols suppress oxidative stress by affecting inflammatory signalling pathways such as mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NFκB) (Chuang & McIntosh, 2011).

2.3. Anti-Inflammatory Activities of Dietary Polyphenols

Inflammatory heat sensation occurs with the increased movement of blood from the veins to the extremities, causing increased redness depending on the amount of erythrocytes passing through the area. Edema is the result of fluid migration from dilated blood vessels to surrounding tissues, infiltration of cells into damaged areas, and accumulation in connective tissue in a long-term inflammatory response. Pain results from stretching of sensory nerves due to tissue damage or the effects of mediators arising directly from the inflammatory response itself.

Inflammation causes acute inflammation in the skin with *S. Aureus* infection, chronic inflammation in atherosclerosis, damage to the bronchial wall in chronic bronchitis and damage to the joints in rheumatoid arthritis. This situation includes many immune cells such as B-T cells, basophils, neutrophils, and mast cells. In addition, inflammatory lesions also show the presence of specific leukocytes. In other words, the inflammatory process is regulated to ensure appropriate leukocyte accumulation, and this occurs through a series of extracellular mediators such as growth factors, cytokines, cyclooxygenases (thromboxane, prostaglandin, prostacyclins) (Newbould, 1963; Pearson et al., 1961; Winter et al., 1962).

The anti-inflammatory activities of polyphenols can be divided into targets related to arachidonic acid-dependent pathways (cyclooxygenase inhibition, lipoxygenase inhibition, and phospholipase A2 inhibition). In cases independent of arachidonic acid, the production of nuclear factor κB (NFκB), nitrous oxide synthase (NOS) and NSAID-activated gene-1 (NAG-1), type 1 and type 2 cytokines is another target of Polyphenols (Miles et al., 2005).

Polyphenols show antioxidative effects in the arachidonic acid-dependent pathway. Epigallocatechin gallate (EGCG), a polyphenol derivative, is known to reduce COX-2 expression in 12-O-tetradecanoylphorbol-13-acetate (TPA)-stimulated human mammary epithelial cell line, and this may affect the protein kinase and p38 mitogen-activated protein involved in the regulation of COX-2 expression. is due to a decrease in the activation of the kinase (Kundu et al., 2003).

2.3.1. Effects on nuclear factor κB

An important aspect of the body's inflammatory response is NFκB activation (Victor et al., 2004). When NFκB is activated, it is transported to the cytoplasm and induces transcription. As a transcription factor sensitive to redox reactions, it is activated by ultraviolet radiation, free radical inflammatory stimuli, and cellular stress factors. After activation, it induces proliferation, apoptosis, metastasis and inflammation with more than 200 genes. Thus, agents that can suppress NFκB activation have therapeutic, delaying and preventive effects on diseases. NFκB, which is sensitive to redox reactions, is regulated through the balance of pro-oxidative and anti-oxidative mechanisms. When antioxidant mechanisms are weak, their overexpression promotes cellular stress. Monocytic cells and macrophages are involved in a cellular response to infection, inflammation, and other associated innate and adaptive immune effects. Lipopolysaccharides are an effective stimulator of the secretion of many proinflammatory cytokines in macrophages, such as interleukin 1β, TNFα, prostaglandin and nitric oxide. In recent years, Djoko and colleagues (Djoko et al., 2007) reported in their studies that resveratrol, a polyphenol, reduces the use of nitric oxide caused by lipopolysaccharide.

2.3.2. Effects on NSAID-activated gene-1

Another COX-independent mechanism mediated by compounds induced by NSAIDs in the inflammation response is NSAID-activated gene-1 (NAG-1). NAG-1-protein, which has a wide activation range, is active in cell and differentiation in inflammation-related cancer. The NAG-1 gene shows the activity of transcription growth factor β (TGFβ) superfamily member cytokines. Unlike other members of this family, NAG-1 is stimulated not only by NSAIDs but also by dietary compounds (Baek, 2004).

2.3.3. Neutrophil release

Resveratrol, found in red grapes and grapevines as a polyphenol, is known to inhibit lipopolysaccharide-induced respiratory neutrophilia and increase the inflammatory response through an NFκB-independent pathway. In a mouse model, resveratrol inhibits cytokine- and TNFα-induced increases in neutrophil chemoattractant-1 levels in lung tissues (Birrell et al., 2005). Resveratrol (5-10 mg/kg/day) used for the inflammatory response reduces the neutrophil infiltration index and IL-1β level, and as a result of immunohistochemical analysis, it was determined that the expression level of COX1 did not change and the expression of COX2 decreased (Martín et al., 2006).

2.3.4. Nitric oxide and inducible nitric oxide synthase interactions

In an experimental mouse study on septic shock, Kang and colleagues investigated the effectiveness of glabridin and isoflavenin. It was determined that these polyphenol-derived flavonoids had an inhibitory effect on melanogenesis and inflammation. Additionally, these compounds were reported to have antinephritic, antimicrobial, and antiarteriosclerotic effects. This study shows that nitric oxide (NO) production and expression of the reducible nitric oxide gene in macrophages are inhibited.

Nitric oxide overproduction is associated with the pathogenesis of many conditions such as septic shock and subsequent multiorgan failure. In addition, induction of the reduced NO gene is thought to be important in tissue damage and vasodilation. Additionally, experimental studies report that glabridin attenuates dose-dependent lipopolysaccharide-induced increases in plasma concentrations of nitric oxide and TNFα, and it has been reported that glabridin reduces lipopolysaccharide-based NO production and reduced NO gene (INOS) expression in macrophages by inhibiting NFκB/Rel activation. In addition to this inhibitory effect, glabridin was also reported to have antioxidative activity that inhibited the increase in the formation of reactive oxygen species in cells treated with hydrogen peroxide (Kang et al., 2005). In another study, Dos Santos and colleagues examined the antipyretic, anti-inflammatory and analgesic activities of the natural polyphenolic compound chlorogenic acid (CGA). At the end of the study, it was concluded that inflammatory mediators such as TNFα and NO may be due to the protective effect of CGA in peripheral synthesis and release.

3. CONCLUSIONS

Polyphenols are compounds with many potential properties such as anti-inflammatory, antioxidant, antineoplastic, anti-aging and anti-cancer. Polyphenols are gaining importance with their effects on many metabolic processes and their wide range of applications in different pathological conditions. Oxidative stress mediates inflammatory processes that play a role in many chronic diseases. Clinical studies report that oxidative stress and inflammation associated with the production of ROS species play a role in the development of many diseases, including chronic diseases. In vivo and in vitro studies suggest that dietary polyphenols may be beneficial in the treatment of diseases. In addition, there is a need to better clinically define the protective and therapeutic effects of polyphenols, and it is thought that these studies will be useful in the development of compounds with anti-inflammatory effects.

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CHAPTER 2

USE OF MEDICINAL AND AROMATIC PLANTS IN EDIBLE FILMS AND COATINGS

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DOI: https://dx.doi.org/10.5281/zenodo.10454498

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INTRODUCTION

Packaging, the final stage of the food production process, plays a critical role in ensuring the quality and safety of the finished product (Kapetanakou, et al., 2014). Foods deteriorate due to various factors during production, storage, and transportation. (Topuz and Boran, 2018). Packaging has versatile functions such as delaying deterioration by protecting the product from external factors, extending shelf life, and maintaining quality and reliability in packaged foods. (Ahmad et al., 2012 Kumar et al., 2022). Various types of packaging are used for purposes such as preventing quality losses, ensuring food integrity, and informing the consumer (Topuz and Boran, 2018). Plastic, paper, glass, metal and composites are traditional food packaging (Kumar et al., 2022). Plastic packaging, constituting approximately 70% of the total packaging materials, is widely used in the packaging of foods (Hammam, 2019). The impact of packaging on the environment as well as the product is important (Emaeilpour and Rajabi, 2016). Plastics such as polyethylene, polypropylene and polyethylene terephthalate, which are food-grade plastics obtained during the processing of oil and called petroleum-based products, are not environmentally friendly (Sundqvist-Andberg and Akerman, 2021). Today, pollution caused by plastic packaging has reached alarming proportions (Gheorghita Puscaselu et al., 2021). Furthermore, studies conducted in recent years have proven that plastic packaging adversely affects human health due to the interaction between foods and packaging (Hammam, 2019). Developments in food packaging have brought about the use of new packaging techniques instead of synthetic packaging (Pal et al., 2019; Díaz-Montes and Castro-Muñoz, R. 2021). Edible films and coatings are one of these significant developments. Edible films are environmentally friendly materials as they are produced from agricultural-origin, natural, and biologically recyclable substances, contributing to environmental preservation by not polluting the environment (Debeaufort et al., 1998; Díaz-Montes and Castro-Muñoz, R. 2021).

1. EDIBLE FILM AND COATING

Food packaging materials derived from natural sources, as opposed to synthetic ones, are known as edible films and coatings. These materials can be put to the outside or inside of food products to safeguard them and prolong their shelf life (Krochta and Mulder-Johnston 1997; Miller ve Krochta 1997). In recent years, interest in edible films and coatings has increased due to their environmental friendliness, easy accessibility and cost advantages (Bourtoom, 2008; Sharma et al., 2016). Edible films and coatings attract a lot of attention today because they provide a barrier against moisture, oxygen, carbon dioxide and lipids between food and the surrounding atmosphere (Bourtoom, 2008; Kapetanakou, et al., 2014). Edible films and coatings reduce undesirable color formation, lipid oxidation, and loss of taste and aroma compounds in foods (Tural et al., 2017; Hammam, 2019). They also improve the quality and shelf life of the food by ensuring that components such as antioxidants, antimicrobial substances, pigments, ions that stop browning reactions and vitamins are kept in the packaging. (Kaya and

Kaya 2000; Guillard et al., 2003; Silva-Weiss et al., 2013; Tural et al., 2017).

Edible film is defined as applying pre-prepared thin edible material on food components or food itself. Edible coating is often characterized as a thin layer of edible material created on a food (Kester and Fennema 1986). The main difference between edible films and coatings is that edible coatings are generally applied to food by dipping method or spraying, while edible films are prepared as a solid layer and then the food is wrapped with this film (Tural et al., 2017). Edible films and coatings materials are extracted from plant and animal sources in the form of polysaccharides, proteins and lipids. These materials are used either individually or in varying combinations (Caner and Küçük, 2004; Shiekh et al., 2013; Chhikara and Kumar, 2022). However, their use in edible coatings is limited due to the impermeable natural waxy structure of animal-derived materials, the allergic conditions they cause or the religious beliefs of consumers (Shiekh et al., 2013). For this reason, coatings using components obtained from plant sources are more widely used (Hashemi et al., 2017; Nawab et al., 2017).

2. USE OF MEDICINAL AND AROMATIC PLANTS IN EDIBLE FILMS AND COATINGS

Interest in natural additives has increased in the food industry due to the understanding of the negative effects of synthetic additives on health. Plant materials are a good source of obtaining natural additives (Silva-Weiss et al., 2013). Plants that are used as medicine to treat illnesses, preserve health, or prevent sickness are known as medicinal and aromatic plants. A pleasant scent and taste are provided by aromatic plants, whilst medical plants are utilized in sectors like nutrition, cosmetics, body care, incense, or religious activities (Faydaoğlu and Sürücüoğlu, 2011). Medicinal and aromatic plants can produce a broad range of chemical substances that serve crucial biological roles (Laranjo et al., 2022). Medicinal and aromatic plants are good sources of natural antioxidants and contain various polar and non-polar phenolic compounds (Miguel, 2010; Charles, 2012). In recent years, because of their antibacterial and antioxidant properties, medicinal and aromatic herbs are increasingly used in edible coatings and films (Cerqueira, 2019). Their antioxidant activities are due to compounds such as vitamin C, phenolic compounds, carotenoids and vitamin E (Calucci et al., 2003; Shahidi and Naczk, 2004; Turhan and Üstün, 2006). In addition, many non-volatile compounds they contain, such as carnosol, quercetin, caffeic acid and rosmarinic acid, are known to be good free radical scavengers (Zheng and Wang, 2001; Calucci et al., 2003). Consumer interest in essential oils derived from aromatic and medicinal plants is growing as one of the natural antimicrobial agents utilized in food packaging (Haworth, 2003; Skerget et al., 2005, Seydim and Sarikus 2006; Mohammed et al., 2020). Below are some examples related to the use of medicinal and aromatic plants in edible films and coatings.

Maurya et al., (2013) reported in their study that the essential oil obtained from turmeric has antimicrobial effects against *Bacillus* *subtilis, Staphyloccoccus aureus* and *Corynebacterium diphtheriae* bacteria, while the essential oil obtained from clove, cinnamon and thyme has antimicrobial effects against *Listeria monocytogenes* and *Salmonella enteritidis* bacteria. In a study investigating the inhibitory effects of rosemary extract on bacterial growth, it was found that after 24 hours at 30°C, rosemary extract had no antimicrobial effect on gram-negative bacteria such as *Escherichia coli, Salmonella enteritidis*, and *Erwinia carotovora*. However, it completely inhibited *Listeria monocytogenes, Bacillus cereus, Leuconostoc mesenteroides*, and *Streptococcus mutans* (Del Campo et al., 2000). In studies examining the shelf life of shrimp (Cadun et al., 2008) and turkey meatballs (Karpińska-Tymoszczyk, 2008) marinated with rosemary extract, it was found that the shelf life of the trial groups with rosemary extract increased compared to the control group. In studies examining the effects of *Urtica diocia* and thyme, which contain natural antioxidants, on the shelf life of *Oncorhynchus mykiss* fillets, it was found that the shelf life of the fillets was extended compared to the control groups (Hisar et al., 2008; Mexis et., 2009).

Smith et al., (1998) determined that thyme, clove, cinnamon and bay essential oils have bacteriostatic effects against foodborne pathogens (*E. coli, S. aureus, Salmonella enteridis, L. monocytoges, Campylobacter jejuni*). Rojas-Grau et al., (2007) found in their study that films prepared from alginate and apple puree containing thyme, cinnamon, lemon verbena (*Lippia citriodora* L.) essential oils and the main components of these essential oils, carvacrol, cinnamaldehyde and citral, showed significant antibacterial effects against *E. coli* O157:H7. Ayana and Turhan (2009) applied methylcellulose-based films containing olive leaf extract to sliced kashar cheese to prevent the growth of *S. aureus*. As a result of the study, it was determined that the number of *S. aureus* decreased by 24.5% in kashar cheese slices coated with methylcellulose-based film containing 1.5% olive leaf extract. In their study, Torlak and Nizamlıoğlu (2011) investigated the antibacterial activities of edible films containing thyme and clove essential oils and chitosan against S. aureus and *E. coli* O157:H7 and found that the antibacterial effects of all film types were significant.

Kavas et al., (2015) used a film containing whey isolate containing 1.5% thyme and clove essential oils and 1.5% sorbitol in the coating of traditional semi-hard cheddar cheese. In the study, it was stated that the film containing thyme and clove essential oil had positive effects on the physical and chemical properties of kashar cheese. It was also observed that films containing essential oil reduced the levels of *E. coli* O157: H7, L. monocytogenes and S. aureus during daily storage. In the study conducted by Gómez-Estaca et al., (2009), the antioxidant capacities of films to which thyme and rosemary essential oils were added were investigated and it was determined that thyme showed more antioxidant activity than films to which rosemary oil was added. In a study examining the effects of chitosan coatings containing rosemary and thyme oils on the ripening index, water loss, sensory, and microbiological properties of cheeses, it was determined that, according to sensory evaluation results, the best application in terms of taste and aroma was in double-coated cheeses containing chitosan-thyme oil (Embuena et al., 2016). Jouki et al., (2014) prepared edible films from quince seed mucilage by adding thyme essential oil at different concentrations (0%, 1%, 1.5%, 2% v/v). Antibacterial activity, physical and mechanical barrier properties and antioxidant properties of the prepared films were evaluated. While researchers detected an increase in both antioxidant activity values and phenol content due to increasing concentrations of thyme oil, they reported that films containing 1% thyme oil showed effective inhibitory properties against all test microorganisms.

Naga Mallika et al., (2020), nanoemulsions prepared from ginger and cardamom essential oils were added in 10, 20 and 50 µl amounts to the film formulation solution prepared by adding sodium alginate (2%) and glycerol (4%). The addition of ginger oil and cardamom essential oil to the films significantly increased antioxidant activity in relation to rising concentrations compared to control films. Raybaudi-Massilia et al., (2008) inoculated melon slices with Salmonella enteritidis (108 cfu/ml) and then coated the natural antimicrobial substances, cinnamon, palmorasa and lemon verbena (*Lippia citriodora* L.) essential oils and malic acid by combining them with an alginate-based edible film. Then, they examined its effects on shelf life during storage. At the end of the research, they observed significant decreases in the population of *S. enteritidis* inoculated into melon samples to which edible film was applied. Benitez et al., (2013) coated kiwis with aloe vera-based edible film and found that textural properties were better preserved compared to the control sample, and respiratory rate and microbial load decreased. In a study where a thymol-containing soy protein-based coating was applied to strawberries, it was observed that compared to the control samples, coated samples exhibited a prolonged inhibition of total colony, mold, and yeast development. Additionally, the content of ascorbic acid and chroma value were found to be preserved for an extended period. (Amal et al., 2010).

3. CONCLUSION

The use of medicinal and aromatic plants in edible films and coatings has yielded successful results by offering various advantages. By incorporating these plants into the compositions of edible films and coatings, they contribute to both the health and flavor enhancement of food products. Particularly, the antioxidant and antimicrobial properties of medicinal plants carry the potential to extend the shelf life of foods and reduce the risk of microbial contamination. Additionally, the extracts and volatile oils from aromatic plants have the capacity to impart natural aroma and taste to foods through edible films and coatings. This represents a significant advantage in providing consumers with more appealing and healthier products. Furthermore, the use of medicinal and aromatic plants can enhance the environmental sustainability of edible films, replacing traditional packaging materials. In conclusion, the utilization of medicinal and aromatic plants in edible films and coatings presents a successful approach from both functional and environmental perspectives.

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CHAPTER 3

EFFECTS OF MYB TRANSCRIPTION FACTORS ON SECONDARY METABOLITES IN PLANTS

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DOI: https://dx.doi.org/10.5281/zenodo.10454515

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INTRODUCTION

Transcription factors (TFs) are known as trans-acting factors capable of binding connections with cis-acting molecules located in the promoter regions of genes. Consequently, these proteins are encoded by genes that are activated by genes actively expressing their transcription (Zhang et al., 2007). A major pathway controlling physiological aspects of plant biological processes is the regulation of gene expression at the transcriptional level. While a single regulatory factor can govern specific gene expression, it can also be influenced by multiple regulatory factors in this process (Krizek and Meyerowitz, 1996; Honma and Goto, 2001).

TFs, vital components of stress mechanisms in plants, regulate the functional gene expression of plants. During protein synthesis, TFs comprise four regions: transcriptional regulatory region, DNA binding domain, oligomerization domain, and nuclear localization signal domain. These regions significantly impact the structural characteristics of TFs (Meshi and Iwabuchi, 1995; Chen et al., 2009). The specificity of DNA binding regions leads to the classification of TFs into different families. For instance, in plants, there are four families associated with stress resistance: WRKY, bZIP, AP2/ERF, and MYB. Among these factors, MYB transcription factors are both abundant and widely distributed in advanced higher plants. This family, crucial in terms of functionality, plays significant roles in the plant's stress mechanism (Liu et al., 2008).

First identified in avian myeloblastosis virus (AMV), the initial MYB TF is v-Myb (Weston and Bishop, 1989). In plants, animals and fungi, this TFs was subsequently found (Rosinski and Atchley, 1998; Stracke et al., 2001). In the model organism *Arabidopsis thaliana* around 1600 TFs have been identified which represents approximately 6%, of this plant genome. (Yanhui et al., 2006). Typically, members of the MYB TF family members are categorized into four subclasses based on their protein domain structures: 1R-MYB, 2R-MYB, 3R-MYB, and 4R-MYB (Paz-Ares et al., 1987) (Figure 1). These TFs exert influence on various biological processes in plants, including defense-stress response, seed and flower development, as well as the regulation of both primary and secondary metabolites (Jin and Martin, 1999; Liu et al., 2015; Ramya et al., 2017).

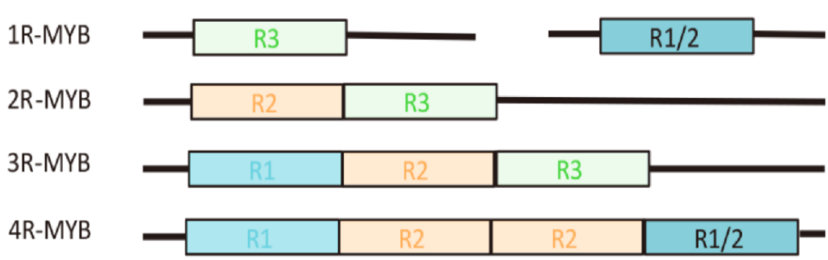

Figure 1. Classification and structural representation of MYB TFs in plants. In plants, MYB TFs have been identified with one to four MYB domain repeats. (Cao et al., 2020).

Plant MYB proteins are classified into three main groups: MYB-related proteins, R1R2R3-MYB, and R2R3-MYB, which typically contain a single MYB repeat, forming a heterogeneous group. The expansion of the MYB family in plants has occurred selectively, notably through the extensive R2R3-MYB family. Within the *Arabidopsis* genome, there are 138 classified as R2R3-MYB, 52 as MYB-related, 5 as R1R2R3-MYB, and 2 as atypical MYB genes. R2R3-MYB proteins are plant-specific and being represented by over 100 members in both dicot and monocot genomes, indicating their prevalence among plant species (Hong, 2016).

Previous studies have shown that MYB TFs influences various aspects of plants, such as the development of secondary metabolites, responses to environmental factors and responses to hormones. MYBs has been shown to function as a regulatory element in cell cycles, differentiation and morphogenetic processes (Uimari and Strommer, 1997). There are many studies that can be cited as examples of these effects. The AtMYB18/LAF1, AtMYB30 and AtMYB38 TFs in *A. thaliana* have been reported to affect hypocotyl elongation through different regulators (Yang et al., 2009; Froidure et al., 2010). In a study in rice and barley, MYBS1 and MYBGA TFs interact with the MYB DNA complex to increase the expression of *α-amylase* genes and stimulate endosperm formation and seed germination (Hong et al., 2012). Overexpression of *MYB10.1* in peach, affects flower development by repressing *NtMYB305* (Rahim et al., 2019). In *Malus domestica*, MdMYB39L is involved in regulating pollen tube development and stamen growth, which are important for pollination in flowers (Meng et al., 2017).

MYB TFs play a role in the regulation of gene expression. While their own expression is regulated by upstream genes, this family of TFs regulates the expression of downstream genes. The WD40 protein

TTG1 plays a key role in several metabolic pathways of these TFs (Ramsay et al., 2005; Mishra et al., 2012). The fact that MYB TFs regulate not only functional genes but also other TFs is another important feature of MYB TFs. For example, NACs are regulated by MYBs during secondary wall synthesis in *A. thaliana* (Zhou et al., 2009).

Plant secondary metabolites encompass compounds like flavones, flavonoids, flavonones, proanthocyanins, stilbenes, phenolic compounds, monolignols, terpenes and alkaloids. These compounds serve essential roles such as enhancing the plant's mechanical strength, acting as signaling molecules, pigment formation, and functioning as defense agents against ultraviolet radiation. Among the transcription factors found in plants, the v-Myb myeloblastosis viral oncogene homolog (MYB) family of transcription factors is one of the most extensive. MYB transcription factors play a crucial role in regulating the biosynthesis of secondary metabolites in plants (Figure 2).

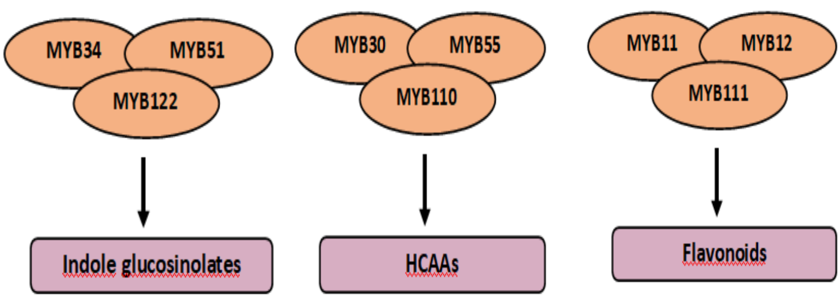

Figure 2. TFs interact to regulate secondary metabolism. Transcription factor complexes are regulators of the various secondary metabolites' biosynthesis in protein interaction (Meraj et al., 2020).

1. Role of MYB TF in the Regulation of Secondary Metabolic Pathways

Secondary metabolites in plants are vital compounds that influence significant regulatory mechanisms and cellular adaptation. Studies have aimed to elucidate the regulatory functions of the MYB TFs, particularly in economically important crops such as rice, soybean, maize, and apple, regarding secondary metabolites (Du et al., 2009; Cao et al., 2013). For instance, ZmMYB31 and ZmMYB42 TFs in *Zea mays* and EgMYBB1 in *Eucalyptus gunnii* have shown the ability to suppress lignin biosynthesis (Legay et al., 2007; Sonbol et al., 2009). In *Malus domestica*, MdMYB3, MdMYBA, and MdMYBB1 TFs can control red-pigmented anthocyanin synthesis (Takos et al., 2006; Ban et al., 2007). In *A. thaliana*, AtMYB11, AtMYB12, and AtMYB111 activate genes encoding flavanone-3-hydroxylase, chalcone, chalcone synthase, flavanol synthase and isomerase enzymes, which determine flavonoid content (Misra et al., 2010; Pandey et al., 2014) (Figure 2). Limited studies have investigated the impact of MYB TFs on secondary metabolites in medicinal plants (Cao et al., 2020; Ma et al., 2023) (Table 1).

Table 1. MYB TFs involved in some biological metabolism in plants.

Plant Name	**Transcription Factor**	**Fonctions of plant metabolism**	**References**
Arabidopsis thaliana	AtMYB18/LAF1, AtMYB30, and AtMYB38	Hypocotyl elongation	Froidure et al., 2008
	AtMYB118/PGA37 and AtMYB115	development of seed embryo	Wang et al., 2009
	AtMYB59, AtMYB68, and AtMYB77	Regulation of hormones and their networks in root development	Mu et al., 2009
	AtMYB24, AtMYB33, AtMYB35/TDF1, AtMYB125/DUO1, AtMYB65, AtMYB99, AtMYB108/BOS1	Formation of reproductive organs development	Phan et al., 2011
	AtMYB16/MIXTA and AtMYB17	Regulation of the morphogenesis of petal epidermal cells and the development of the inflorescence	Jakoby et al., 2008
Triticum aestivum	TaPL1	Increase of anthocyanin synthesis and accumulation	Shin et al., 2016
	MYB3, MYB4, MYB13 and MYB59	wheat’s salt stress response	Sukumaran et al., 2023
Panax notoginseng	PnMYB	Regulation of biotic, abiotic stress and hormone induction	Chen et al., 2023
Panax Ginseng	PgMYB2	regulatory effect in ginsenoside synthesis	Liu et al., 2019
Ginkgo biloba	GbR2R3-MYB	Play a different abiotic stresses and hormonal exposures	Yang et al., 2021
	GbMYB5, GbMYB26, GbMYB31	Play a role in the biosynthesis of flavonoids under stress conditions	Liu et al., 2017
Medicago truncatula	MtMYB134	Regulation of flavonol biosynthesis	Naik et al., 2021

Table 1. (continued)

Plant Name	Transcription Factor	Fonctions of plant metabolism	References
Salvia miltiorrhiza	SmMYB36	Increases tanshinone accumulation and reduces phenolic acid levels	Ding et al., 2017
	SmMYB39	Decreased the accumulation of phenolic acids	Zhang et al. 2013
Papaver somniferum	PsMYB, MYB26-like	Specific role in BIA biosynthesis, biosynthesis of phenylpropanoids	Uimari and Strommer 1997; Gürkök Tan et al., 2023

2. The Involvement of MYB TFs in the Secondary Metabolism of Flavonoids Biosynthesis

Flavonoids constitute a diverse family of secondary metabolites, including anthocyanins such as cyanidin and pelargonidin, isoflavones like genistein and daidzein, flavanols such as catechins and flavonols like myricetin and quercetin (Saito et al., 2013). Through modifications such as methylation, hydroxylation, acylation and glycosylation, this family plays an effective role in plant color and diversity. Flavonoids, particularly important for pigmentation, influence the plant pollination mechanism and enhance plant resistance to pathogenic agents and environmental stress factors (Hichri et al., 2011).

MYB TFs play significant roles in the biosynthetic regulation of flavonoids (Ma and Constabel, 2019). These TFs regulate the expression of multiple genes in the secondary metabolite pathway of flavonoids by activating them. Studies have reported the involvement of MYB TFs in increasing the expression of genes encoding enzymes such as chalcone isomerase, chalcone synthase, and dihydroflavonol alcohol reductase (Wang et al., 2018). Numerous similar studies support this finding. Yuan et al. (2015) reported that the upregulation of *SbMYB8* in *Scutellaria baicalensis* could induce changes in the expression levels of genes associated with flavonoid synthesis. Another study on *Camellia sinensis* indicated that CsMYB4a *n*egatively regulates the synthesis of lignin, phenylalanine, and phenolic acids, in addition to flavonoid synthesis (Li et al., 2017). In a subsequent study conducted on the same plant the following year, it was discovered that CsMYB2 and CsMYB26 regulate the expression of *CsF30H* and *CsLAR*, respectively, and are involved in flavonoid biosynthesis (Wang et al., 2018).

3. Role of MYB TFs in the Terpenoid Metabolic Pathway

The MYB TFs play an important role in regulating the terpenoid metabolic pathways. Terpenoids represent a diverse group of natural compounds widely distributed in plants. These compounds can be categorized into various subgroups, including monoterprenoids, diterpenoids, sesquiterpenoids, triterpenoids, and irregular terpenoids based on their structural units. For example, in *Mentha spicata*, the R2R3-MYB subgroup 7 member MsMYB has been identified as a novel negative regulator of monoterprenoid synthesis. Its expression in tobacco reduces the production of sesquiterpene and diterpene-derived metabolites (Reddy et al., 2017). Similarly, in *Salvia miltiorrhiza*, SmMYB36 acts as an activator of terpenoid synthesis that is specifically involved in tanshinone synthesis (Ding et al., 2017). The MYB TF CrBPF1 in *Catharanthus roseus* can regulate the production of terpenoid indole alkaloids by binding to the Str promoter (Li et al., 2015).

4. Role of MYB TFs in the Glucosinolate Metabolic Pathway

Glucosinolates (GSLs) are significant secondary metabolites found in substantial amounts, especially in members of the Brassicaceae family, generally involved in the formation of sharp smells and tastes in plants. Studies suggest the involvement of MYB TFs in the biosynthesis of GSLs, believed to play a role in defense mechanisms against harmful insects in plants (Augustine et al., 2013; Robin et al., 2016). One such study reports the regulation of aliphatic GSL biosynthesis in *A. thaliana*, primarily by AtMYB28 alongside AtMYB29 and AtMYB76. It has been demonstrated that AtMYB34, AtMYB51, and AtMYB122 regulate the biosynthetic mechanism of indole GSLs (Gigolashvili et al., 2007). Furthermore, these three transcription factors have been reported to serve the same function in Chinese cabbage, a plant known for its intense aroma (Kim et al., 2013). Another study conducted with *Brassica rapa* revealed that BrMYB28.1, BrMYB28.2, and BrMYB28.3 regulate indole, aliphatic, and aromatic GSL biosynthesis under biotic and abiotic stress conditions (Seo et al., 2016).

5. Role of MYB TFs in the Phenylpropanoid Metabolic Pathway

One of the significant secondary metabolites synthesized from phenylalanine catalyzed by the enzyme phenylalanine ammonia-lyase in plants is phenylpropanoids. These metabolites are crucial components of the shikimate pathway, which is highly significant for the biosynthesis of compounds such as flavonols, anthocyanins, proanthocyanidins, coumarins, lignins, and lignans (Fraser and Chapple, 2011). Phenylpropanoids play pivotal roles in plant resistance and tolerance against stressors, contributing significantly to plant growth and development. Additionally, their accumulation in aerial parts of the plant contributes to reproduction and signaling mechanisms through the accumulation of anthocyanins and flavonols. These phenylpropanoids, which are also essential secondary metabolites for human health, exhibit potent antioxidant properties (Rahim et al., 2023).

Studies have highlighted the significant roles of MYB TFs in regulating phenylpropanoids. MYB TFs were shown to act as primary regulators of the structural genes of this biosynthetic pathway in a study elucidating the role of R2R3-MYB TFs in anthocyanin biosynthesis (Rahim et al., 2014). Furthermore, the color diversity of organs in agricultural products can result from mutations such as insertions, deletions, or single nucleotide polymorphisms in the promoter regions of R2R3-MYB TFs. For instance, a 487-bp deletion in the promoter region of the MYB gene leads to a color change in the region surrounding the stone of a peach (Guo et al., 2020). DNA methylation in the promoter region of this transcription factor gene was also shown to control anthocyanin pigmentation (Qian et al., 2014; Jiang et al., 2020).

6. Role of MYB TFs in the Lignin Metabolic Pathway

Lignin is an aromatic heteropolymer synthesized via the phenylpropanoid metabolism. It contributes to stem durability and cellular mechanical resistance in plants. It is well established that MYB TFs play a significant role in lignin biosynthesis. In *A. thaliana*, the MYB83 and MYB46 TFs are direct target genes of AtSND1 (NAM-ATAF-CUC [NAC] domain protein 1), a protein involved in cell wall synthesis. Their induction triggers the expression of MYB58, MYB63, and MYB85, which interact with the AC elements in the promoters of lignin synthesis genes (Zhong et al., 2007; Zhou et al., 2009). Conversely, in another study, it was found that MYB20, MYB42, and MYB43 in *A. thaliana* led to a significant decrease in lignin synthesis and developmental defects (Geng et al., 2020). Similarly, in *Z. mays*, ZmMYB31 and ZmMYB42, in *Panicum virgatum* PvMYB4a, and in *Leucaena leucocephala* LlMYB1 transcription factors have been reported to inhibit lignin synthesis (Sonbol et al., 2009; Shen et al., 2012; Omer et al., 2013).

7. CONCLUSION

The conserved structure of MYB TFs has been revealed by phylogenetic and structural analyses so far. This may be explained by the similarity of their activities in different plants. The structural proteins and biological functions of most MYB TFs are well conserved, especially among angiosperms. In terms of secondary metabolites, the regulatory function of MYB TFs in the flavonoid pathway is very important. Regulated by miRNAs, environmental cues, plant growth regulators, these transcription factors are moving towards a diversity of functional structures and functions.

Currently, the knowledge of plant secondary metabolite mechanisms is limited. It is hoped that future studies on transcriptional factors and genes will elucidate these mechanisms. In conclusion, although MYB TFs have a complex mechanism, increasing the studies on these factors seems to be very important to understand the transcriptional regulation of secondary metabolites in plants of medicinal and agricultural importance.

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CHAPTER 4

MEDICINAL PLANTS IN BREAST CANCER PREVENTION AND TREATMENT

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DOI: https://dx.doi.org/10.5281/zenodo.10454579

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INTRODUCTION

Cancer is the result of cascading genetic and epigenetic changes resulting in apoptosis, uncontrolled cell proliferation, metastasis and angiogenesis (Wang et al, 2013). Even with the ongoing advancements in clinical oncology research, cancer continues to be a serious global health issue (Canbaz T. , 2022). Cancer is the second leading cause of death worldwide after cardiovascular diseases, causing the deaths of approximately 8.8 million people in 2015 (Anonymous, 2018). Approximately 24,400 deaths a day are caused by cancer, one in every six deaths a day. According to the International Center for Research on Cancer, approximately 1 million new cancer cases and 400,000 cancer-related deaths occurred in young adults aged 20-39 in 2012 alone, and annual new cancer cases are estimated to increase to 23.6 million by 2030 (Fidler et al.,2017). Breast cancer is an important health problem worldwide. It has been announced by the American Cancer Society that breast cancer is the second leading cause of death in women after lung cancer. It is also known that steroidal estrogens cause breast cancer and that these compounds are carcinogenic. It has been described that endogenous estrogens cause cancer by stimulating breast cancer-causing cell growth and proliferation through receptors and genotoxic metabolites (Suda and Mitsudomi, 2014; Peer et al., 2007; (Fidler et al.,2017). Due to the serious side effects of chemotherapeutics used in the treatment of breast cancer (Liao et al., 2013; Keklikcioğlu Çakmak, 2022), the isolation of many naturally occurring compounds that may have therapeutic potential and their possible mechanisms of action are being investigated.

A significant amount of the pharmaceuticals used to treat breast cancer come from plants. Through a detoxification process, several of these herbs can shield the body from cancer. By altering hormone and enzyme activity, medicinal plants that change the biological response can help stop the growth of cancer through prevention. By decreasing the negative effects of radiation and chemotherapy, others can assist with the treatment. This section focused on looking at medicinal plants that might be able to treat breast cancer.

Approximately 54% of anticancer medications approved from 1940 to 2002 were either derived from natural products or developed using knowledge inspired by them. Many plant-derived substances are used as active pharmaceutical ingredients in the treatment of numerous illnesses, including cancer (McGrowder et al.,2020; Gomes et al., 2023).

Over the years, natural compounds have shown to be a very effective and practical source of anticancer agents. Their efficacy results in reduced toxicity and recurrent resistance to anti-cancer drugs that target hormones (Bonofiglio et al., 2016; Kumar and Jaitak, 2019). Their capacity to produce anti-proliferative and anti-apoptotic effects on cancer cells, in addition to their immunomodulatory and antioxidant qualities, accounts for these applications. This is done in a way that presents a chemo-preventative feature that is safe for long-term use and can be both prophylactic and therapeutic (Nguyen et al., 2019).

Terpenoids, coumarins, alkaloids, and flavonoids are examples of natural plant compounds that are known to possess strong immunomodulatory properties that are necessary to inhibit or fight cancer cells (Baraya et al., 2017; Topal Canbaz et al., 2023-a; Topal Canbaz et al., 2023-b).

Hormonal problems are frequently the underlying cause of cancer, and bioactive chemicals like phytoestrogens and isoflavonoids can function as endocrine disruptors for these illnesses. According to reports, these plant flavonoids exhibit chemopreventive qualities in addition to estrogenic and/or anti-estrogenic qualities (Kˇrížová et al., 2019; Dietz et al., 2016). They have the ability to prevent the production of free radicals and genotoxic substances that are not dependent on estrogen receptors, as well as the growth and multiplication of cells that are. Additionally, they have the capacity to trigger oxidative stress and the development of cancer by means of estrogen receptor signaling (Bak et al., 2016).

This chapter focuses on the pharmacokinetics and biochemical characteristics of several plants that have chemotherapeutic qualities, including Ginseng, Garlic (*Allium sativum*), Turmeric (*Curcuma longa*), Black cohosh (*Actaea racemose*), *Camellia sinenis* (green tea), Flaxseed (*Linum usitatissimum*) and Black Cumin (*Nigella sativa*) . These well-known plants were chosen because their mechanisms of action have been documented and they are frequently utilized as adjuvants in breast cancer therapy in traditional medicine.

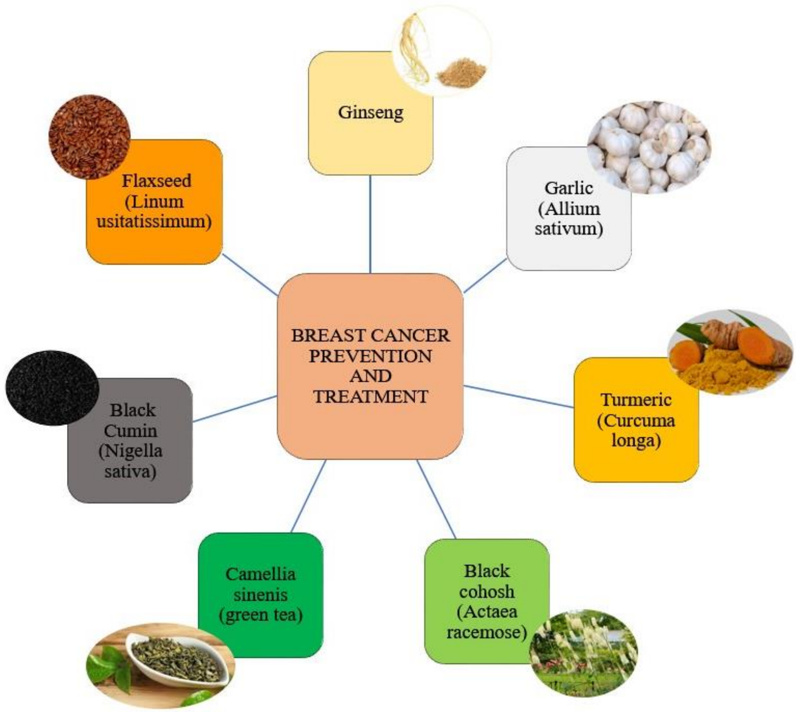

Figure 1. Some important medicinal plants in cancer prevention and treatment.

1. Ginseng

Ginseng is a well-known perennial herb of the Panax genus and Araliaceae family (Popovich et al., 2016). In Chinese, ginseng is known as the "essence of man" and is one of the most widely used herbal remedies in the US. Asian ginseng, sometimes commercialized under the names Panax, Chinese, or Korean ginseng, is the most widely utilized kind. Panax quinquefolius is ginseng that grows in North America. Eleutherococcus senticosus roots are the source of Siberian ginseng, another kind of ginseng that is frequently utilized (Yang et al., 2018; Lu et al., 2009).

Oriental medicine uses ginseng, an age-old medicinal herb, to treat a variety of illnesses. The primary bioactive components of ginseng are saponins; however, their efficacy is diminished because of the numerous glucosyl side chains on their molecules, which block ginsenosides from passing past the intestinal wall and into the blood. In vitro sugar group removal from natural ginsenosides has been a common method of creating uncommon ginsenosides, which have increased pharmacological activity and are easily absorbed by the human body. The rare ginsenosides Rh2 and Rg3 have been licensed for use as medications or dietary supplements to strengthen immunity (Xu et al., 2023). By activating some pathways, ginsenosides Rg3 and Rh2 play anti-inflammatory, anticancer, cardiovascular protective, immunomodulatory, neuroprotective, anti-diabetic, anti-aging, and other pharmacological effects. Through in vitro and in vivo research, ginsenosides Rg3 and Rh2 need to further elucidate other underlying mechanisms of action as prospective medications for the prevention and treatment of many disorders (Wu et al., 2023).

2. Garlic (*Allium sativum*)

Garlic (*A.sativum*) is a functional food with a variety of bioactive components that are used widely in both culinary and medical contexts. Its pungent and aromatic taste renders it a valuable flavoring agent. Garlic, whether raw or crushed, contains a significant amount of chemicals that contain sulfur. Garlic's most significant phytochemicals are diallyl disulfide, diallyl trisulfide, S-allylcysteine, and allicin. Alliin (also known as allyl 2 propenethiosulfinate or diallyl thiosulfinate) is one of these chemicals. In 1990, the US Cancer Institute revealed in its Designer Food Program that garlic is a valuable food with anti-cancer effects (Tusubura et al., 2011).

Garlic is known to contain several sulfur and organic chemicals that may have anticancer properties. These substances interact with several stages of cancer cell development, proliferation, growth, invasion, migration, and metastasis. They do this by acting on multiple pathways, including cell cycle interruption, inhibition of signaling pathways, activation of apoptosis, autophagy, and antioxidant activity. It has been shown in vitro that diallyl disulfide, a product of garlic, slows the growth of human breast cancer cells in culture and lowers the incidence of breast cancer in vivo studies (Tusubura et al., 2011). In vitro research has demonstrated that natural garlic and its derivatives in extracts can induce apoptosis and cell cycle arrest, which can, in a time- and dose-dependent manner, inhibit the proliferation of human breast cancer cell lines (Tusubura et al., 2011; Rauf et al., 2022). In conclusion, these investigations showed that diallyl disulfide, a product of garlic, and human breast cancer cell lines exhibit anti-tumor growth and death in response to these compounds. To further support, especially in human trials, is needed to confirm these findings and to determine the optimal dosage and application methods to definitively talk about its therapeutic or preventive properties on breast cancer.

3. Turmeric (*Curcuma longa*)

Curcuma longa is considered a member of the Zingiberaceae family and a perennial flowering plant. The main active component of this rhizomatous, herbaceous plant, known as turmeric, is found in its roots (Hani et al., 2023). Turmeric's yellow color is attributed to diferuloylmethane, the main curcuminoid with the highest concentration (77%) in turmeric. While a significant amount of research over the last few years has suggested that curcumin has a variety of anticancer effects in different types of cancer by inhibiting cell growth and metastasis, stimulating cell death, and possibly even protecting against the formation of cancer (Hani et al., 2023), other research indicates that curcumin is not a useful substance for either preventing or delaying the development of cancer (de Waure et al., 2023). Curcumin has some drawbacks, such as its in vivo use; it is poorly soluble in water, has a limited systemic distribution, and experiences considerable biotransformation. Using liposome carriers and nanoparticles can enhance its therapeutic potential and efficacy. Even if there are a lot of studies in the literature, there should be more in vivo evidence studies conducted.

4. Black cohosh (*Actaea racemose*)

For the past 60 years, the North American plants known as black cohosh (BC, *Cimicifuga racemosa* or *Actaea racemosa*) has been utilized as a natural remedy for various gynecological disorders and as an alternative to hormone replacement treatment. The long-stemmed herb known as black cohosh has white blossoms and is commonly used to treat menopausal symptoms. Native Americans used to utilize this plant, which is native to eastern United States and Canada, to treat a variety of ailments, such as menopause, premenstrual pain, irregular menstruation, malaria, sore throat, and poor kidney function. BC is becoming ever more popular among women as a "natural" substitute for estrogen replacement therapy. Black cohosh root contains triterpene glycosides, phenolic acids, alkaloids, and tannins. Triterpene glycosides and phenylpropanoids are the supposedly active ingredients in black cohosh. It has been demonstrated that both of the two families of compounds-phenylpropanoids and triterpene glycosides-have strong anticancer effects in vitro (Ploska et al., 2023).

For many years, premenopausal pain, menopausal signs and symptoms like hot flashes, and dysmenorrhea have all been treated and managed with black cohosh (Baber et al., 2005). It is currently unknown which signaling pathways and molecular targets black cohosh affects. According to studies, depending on the dosage and length of therapy, these drugs can trigger either the apoptotic or survival phase of the integrated stress response. According to a specific hypothesis, the phytoestrogens in black cohosh influence central estrogen receptors near the hypothalamic GnRH pulse generator via a negative feedback mechanism, so producing an estrogenic effect (Wuttke and Seidlová-Wuttke 2015). Apart from the estrogenic pathway, a serotonergic mechanism involving selective serotonin reuptake inhibitors is suggested as another way that black cohosh Works (Hoda et al., 2003). Black cohosh has also been shown to have additional effects through different tissue-dependent pathways, such as those involving anti-oxidative, anti-inflammatory, and dopaminergic signaling, which block the proliferation of ER-positive cells (Ruhlen et al., 2008).

Even though black cohosh has been shown to be beneficial in easing anxiety, hot flashes, and other symptoms, many more clinical trials are required to determine whether black cohosh has any anti-cancer effects on patients who have breast cancer.

5. *Camellia sinensis* (green tea)

The four main varieties of tea; green, black, oolong, and white come from the leaves of the *Camellia sinensis* plant and are distinguished by the method of production. Fresh tea leaves are steam-treated as soon as they are harvested in order to prevent the oxidation of green leaf polyphenols during the production of green tea (unfermented).

Green tea is made from the fresh leaves (exposed to heat or hot steam) and buds of the evergreen plant *C.sinensis* (Graham, 1992). Green tea is composed of bioactive polyphenols, and the percentage of polyphenols and caffeine in extracts that are powdered or liquid varies from 45.0 to 90.0%. Polyphenols, flavonoids, flavonols, and other substances such as amino acids, lipids, organic acids, vitamins, polysaccharides, and thiamine are all present in green tea. The main polyphenols that control a variety of genes linked to the development, maintenance, and spread of cancer are called catechins (Corcoran et al., 2012). About forty percent of the dry weight of green tea is made up of catechins, one of the main classes of flavonoids found in the leaves.

Because of its anti-oxidant, anti-mutagenic, and chemopreventive properties, drinking green tea has been linked to the prevention of several cancers, including those of the breast, colon, esophagus, kidney, lung, mouth, pancreas, stomach, and small intestine(Koo and Cho, 2004). Green tea catechins have been the focus of the majority of tea's anticancer research. Green tea used a multimodal strategy to mediate its chemopreventive action. It functioned as a suppressor of the pathways that control the growth and spread of tumors, including cyclooxygenase, lipoxygenases, tumor necrosis factor, and interleukin (Zhang et al., 2020). Several studies examined the potential benefits of drinking green tea or any of its components in lowering the risk of breast cancer (Zhang et al., 2019). Research indicates that women who consume five or more cups of green tea on a weekly basis may have a lower risk of developing breast cancer (Zhang et al., 2020). While some research have shown that frequent use of green tea reduces the risk of breast cancer and improves its treatment outcomes, other investigations have found the opposite (Li et al., 2016; Boggs et al., 2010) .

In conclusion, research conducted both in vitro and in vivo has shown that green tea has anti-cancer properties and works well in conjunction with traditional chemotherapy drugs. The regulation of many intracellular signaling pathways is part of the mechanism of action. Green tea's polyphenols and other constituents may have positive effects by inhibiting the growth of breast cancer, especially in premenopausal women, and preventing its recurrence. However, the mechanisms by which drinking green tea may affect a person's risk of developing breast cancer are still unknown, and epidemiological studies utilizing green tea have yielded conflicting results.

6. Flaxseed (*Linum usitatissimum*)

Linum usitatissimum, commonly referred to as conventional flax or linseed, is a member of the Linnaceae family and has been cultivated for a long time due to its applications in the food and medicinal industries in many different nations (Basch et al., 2007). One of the primary plant sources of essential fatty acids is flaxseed. Its physical composition also includes lignans, minerals like calcium, phosphorus, and magnesium, proteins like glutelin dietary fibers that are both soluble and insoluble (Goyal et al., 2014). Compared to other plants, flaxseed has about 800 times more lignans. Approximately 95% of the lignin content is made up of bioactive, non-nutritional, phenolic compounds called secoisolariciresinol diglucoside. The remaining 5% is made up of lariciresinol, pinoresinol, and matairesinol (Touré and Xueming, 2010) . Studies examining the anti-tumorigenic properties of flaxseed have included animal experiments, such as injecting mice with breast tumor cells. Chen et al. conducted an in vivo study human estrogen receptor (ER) positive breast cancer cells (MCF-7). Significantly lower cyclin D1, Bcl-2, and epidermal growth factor receptor mRNA expressions led to apoptosis and inhibited cell proliferation (Chen et al., 2009). Flaxseed consumption of may help lower the risk of breast cancer, according to observational studies. Taking flaxseed effectively was linked to a considerable decrease in the risk of breast cancer in a clinical research (Lowcock et al., 2013).

Studies carried out in vivo and in vitro have demonstrated that flaxseed has anti-cancer effects because it increases apoptosis and slows the growth of tumors. It has been determined that flaxseed and tamoxifen work in concert to either maintain or increase the efficacy of the chemotherapy drugs. According to clinical research, flaxseed may help individuals with breast cancer experience smaller, less aggressive tumors. Still, additional clinical studies are required to validate the advantages of flaxseed in the management of breast cancer.

7. Black Cumin (*Nigella sativa*)

Nigella sativa, commonly referred to as black cumin, is an annual growing plant that belongs to the Ranunculaceae family and is used medicinally. The seeds of *N. sativa* contain a variety of active components. The primary biologically active ingredient in *N. sativa* is thymoquinone. *Nigella sativa* seeds are used medicinally and contain an essential oil primarily composed of thymoquinone, which has antidiabetic, anti-cancer, anti-inflammatory, hepato-protective, anti-microbial, immunomodulatory, and antioxidant qualities (Tavakkoli et al., 2017; Badary et al., 2003).

Thymoquinone has been found in numerous studies to prevent carcinogenesis through a variety of molecular mechanisms. Additionally, there is evidence that in vitro applications of the drug cause apoptosis in a number of breast cancer cell lines (Wong, 2011; Sundaravadivelu et al., 2019). MDA-MB-468 and T-47D breast cancer cells undergo apoptosis when exposed to thymoquinone (Goyal et al., 2017). Thymoquinone's anti-apoptotic action through the modulation of tumor suppressor genes is a significant factor in chemoprevention (Rajput et al., 2013). However, because to its low water solubility and hydrophobic qualities, its application is restricted Pathan et al., 2011). Thymoquinone's chemotherapeutic potential may be enhanced by mixing it with traditional chemotherapy drugs. Through a variety of molecular pathways, thymoquinone reduced the growth of breast cancer cells in both animal models and culture tumors. Its transport and anti-cancer efficacy may be enhanced when combined with traditional chemotherapy medications or when a very low dosage is enclosed in lipophilic biogels or nanoparticles. Expanding research in vitro and in vivo as well as doing clinical studies is crucial for understanding thymoquinone, a promising chemotherapeutic medication that may be used to treat breast cancer.

8. CONCLUSION

Breast cancer is the most common form of cancer in women and is the second most typical reason for cancer-related mortality among females. Thus, much more work has to be done in the areas of primary breast cancer prevention and prevention of breast cancer recurrence in breast cancer survivors, even though treatment and early diagnosis have made some little progress in these areas. This chapter provides a detailed explanation of the preventive and therapeutic capabilities of some significant plants against breast cancer. The research showed that these plants have anti-cancer properties both in vitro and in vivo. It also showed that these properties and their mechanisms of action involve the prevention of angiogenesis, apoptosis, tumor growth, metastasis, and cell survival pathways.

Numerous human cancer cell lines and, to a lesser degree, animal tumor models are the focus of these plants' chemopreventive properties. Consequently, even if the data suggest that these plants have broad anti-cancer effects when used as therapies, care should be taken when interpreting the results until clinical study data can support them. Important confirmation of the medicinal effects of these plants should come from more clinical research incorporating trials and group human studies.

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CHAPTER 5

OVERVIEWS OF MEDICINAL PLANTS EFFECTIVE ON DIABETES

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DOI: https://dx.doi.org/10.5281/zenodo.10454595

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disorder that affects many populations worldwide. Basically, insulin secretion disorder is a hyperglycemia-induced disorder caused by errors in the mechanism of action of insulin. It is estimated that the number of people diagnosed with DM in the world will reach 366 million by 2030. Although the cases of DM are increasing day by day, insulin and oral medications cannot provide a successful treatment. Plants have been used as a source of medicine since ancient times. It is reported in Ayurveda and some Indian literature that plants are used to treat many diseases of the approximately 250,000 plant species known in nature, only about 1% are used pharmacologically, and very few of these plants are used for anti-diabetes. For this reason, systematic studies on the use of plants with medicinal efficacy in the fight against DM are still needed today.

DM is a disease that occurs with the disruption of carbohydrate, protein and fat metabolism as a result of abnormality in the activity of the insulin hormone secreted in the pancreas (Pareek et al., 2009). It is characterized by chronic hyperglycemia. Symptoms of dry mouth, excessive urination, ketonuria and ketonemia are frequently observed. (Craig et al., 2009). DM; It shows microvascular complications such as retinopathy and neuro-nephropathy, and macrovascular complications such as heart attack, peripheral vascular diseases and stroke, and is known to be directly related to serious mortality and morbidity (Galicia-Garcia et al., 2020).

Hyperglycemia, known as the main symptom of diabetes, creates reactive oxygen species (ROS) that cause disruption of membrane structure and lipid peroxidation. These types of ROS are responsible for the development of major secondary complications in diabetes. Antioxidant systems protect β cells against oxidation by inhibiting lipid peroxidation. Flavonoids, tannins, and vitamins C/E are compounds containing natural antioxidants and prevent the formation of ROS species by protecting the functions of β cells.

According to the etiology of DM, it is divided into two main types: Type 1 diabetes mellitus "Juvenile Diabetes Mellitus" and Type 2 diabetes mellitus "Adult Type". Type 1 DM occurs mainly in childhood due to autoimmune-mediated destruction of pancreatic β cells and insulin hormone deficiency. Type 2 DM is generally seen in adults and the elderly and is mainly characterized by insulin resistance or insulin secretion disorder (Patel et al., 2011).

Another type of DM is gestational diabetes, which occurs during pregnancy. It is also often referred to as maturity-onset diabetes, with defects in pancreatic β-cell function or insulin secretion. In addition, neonatal type diabetes is a type of insulin-dependent disease that occurs as a result of abnormal blood sugar levels in the first three months of life. This kind; It is associated with growth retardation and chromosomal anomalies. Another type is mitochondrial diabetes (MT-DM), the most prominent symptom of which is deafness and is characterized by a deficiency of autoimmune beta cells. In type diabetes associated with cystic fibrosis, insulin hormone deficiency is observed, but insulin resistance and glucose tolerance contribute to increased infections during the disease. In some cases, diabetes may occur as a result of environmental factors such as stress or the use of medications such as dexamethasone, glucocorticoids, cycloporine, L-asparaginase, or risperidol and ziprasidone (Craig et al., 2009).

1. DIABETES MELLITUS PATHOPHYSIOLOGY

DM complications are mediated by some oxidative stress processes such as increased ROS production and impaired antioxidant system. Increased lipid peroxidation contributes to the development of diabetes by causing changes in enzymes involved in antioxidant mechanisms and impaired glutathione mechanism (Dewanjee et al., 2009). Additionally, free radical species are involved in the pathogenesis of various diseases, including diabetes (Bagri et al., 2009). Excessive production and accumulation of glycosylation products contribute to complications such as neuropathy, nephropathy, and retinopathy through a number of pathological differences (Ding et al., 2010).

The most important hormones that maintain the balance of blood sugar levels are 95nsülin and glucagon. Imbalances in hormone levels in the body cause blood sugar to increase, and the increased glucose in the blood is excreted in the urine along with other minerals (Babili et al., 2013). Destruction of pancreatic β cells occurs by T cells in diabetic patients, and up to 90% of the cells become symptomatic when destroyed. Serological markers such as β cell, glutamic acid decarboxylase (GAD), Immunoglobulin A-2β, Immunoglobulin A-2 or insülin autoantibodies are present in approximately 90% of individuals when hyperglycemia is diagnosed (Craig et al., 2009).

2. DIABETES MELLITUS TREATMENT

DM treatment is considered the most fundamental problem in the world. Although oral hypoglycemic agents and exogenous insulin supplementation are used as a treatment option for diabetes, they also have some side effects, and these side effects cause changes in the course of the disease (Venkatesh et al., 2010).

2.1. Insulin

Insulin is a polypeptide consisting of amino acid chain A and amino acid chain B connected by two disulfide bridges, weighing approximately 6 000 Da. There is approximately 8-10 mg of 96nsülin in the pancreas of a healthy person. Since the insulin hormone is inactivated by digestive enzymes, it is not suitable for oral use. Insulin hormone is broken down in the liver and kidneys under normal conditions. The amount of 96nsülin secreted during the day in a healthy person is approximately 40 units. The amount of 96nsülin required to stabilize diabetes varies from patient to patient and depending on the time administered (Babili et al., 2013).

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2.2. Oral medications

Oral medications used insulin treatment of DM are used alone or in combination with sulfonylureas, glucosidase inhibitors and glinides. However, most of these oral antidiabetic drugs have various side effects (Meenakshi et al., 2010; Pareek et al., 2009). Sulfonylureas are used effectively in the treatment of uncontrolled diabetes. This group includes drugs such as tolbutamide, glibenclamide, chlorpropamide, and tolazamide, and the absorption of these drugs from the intestine is rapid (Babili et al., 2013).

Antidiabetic drugs produced from medicinal plants are frequently preferred in the treatment of diabetes due to their positive biological activities (Ding et al., 2010). Many herbal form drugs are used in the treatment of diabetes such as Diabecon, Pancreas tonic 180 cp, Diasulin, bitter gourd powder, Chakrapani, Diacare, Gurmar powder, Diabeta (Modak et al., 2007**).**

3. HERBAL REMEDIES FOR DIABETES

It is known that herbal medicines are frequently preferred due to their curative effects for diseases, and the 97nsül population is generally dependent on traditional medicines (Feshani et al., 2011; Meenakshi et al., 2010). In ethnomedical practices, many medicinal plants and formulations of these plants are used in the Ayurvedic medical system (Pareek et al., 2009). There are approximately 800 plants with antidiabetic potential (Venkatesh et al., 2010; Patel et al., 2011; Babili et al., 2013). Even though many synthetic drugs have been developed 98nsülin treatment of diabetes, very few drugs are available 98nsülin treatment of diabetes (Dewanjee et al., 2009). There are approximately 200 pure blood sugar regulating compounds of plant origin. These compounds are known as carbohydrates, alkaloids, flavonoids, glycosides, terpenoids, steroids, amino acids, phenolic compounds and iridoids (Babili et al., 2013). A number of plants have been reported to potentially have antidiabetic activity. *Momordica charantia*, *Pterocarpus marsupium*, *Trigonella foenum* and *greacum*, insülin dependent/non-insulin dependent diabetes; It is frequently used in patients with diabetic retinopathy and neuropathy. Among these ethnobotanical plants, the plants with the strongest hypoglycemic effects are *Lamiaceae*, *Liliaceae*, *Leguminoseae*, *Cucurbitaceae*, *Asteraceae*, *Rosaceae*, *Moraceae*. These plants have also been tested experimentally with alloxan-induced diabetic rat models (Bnouham et al., 2006).

3.1. *Acacia arabica*

Extracts of *Acacia arabica* bark prepared with chloroform are known to significantly reduce serum glucose levels in DM rats by 250-500 mg/kg for two weeks. It restores total cholesterol, triglyceride, high-density lipoprotein (HDL) and reduces low-density lipoprotein (LDL) level. Additionally, extracts obtained from *Jatropha curcus* leaves, *Tinispora cordifolia* stem *Benincasa hispida* fruit and *Ocimum sanctum* leaves have been reported to have similar effects on diabetic rats (Patil et al., 2011).

3.2. *Achyranthes rubrofusca*

Anti-diabetic activities of aqueous and ethanol extracts of the leaves of the *Achyranthes rubrofusca* plant were investigated in a diabetic rat model. In rats treated with diabetes, levels of blood sugar have been substantially reduced versus controls after treatment. In addition, the level of pancreatic enzymes that play a role in oxidative stress, such as SOD and CAT, and glutathione were significantly increased (Geetha et al., 2011).

3.3. *Andrografis panikulata*

Ethanol extract of *Andrographis paniculata* reduces blood glucose levels when administered orally at a 99öşe of 100-200 mg/kg for 30 days of treatment. In addition, phospholipids, which have antidiabetic properties, also regulate the levels of alanine transaminase, glycosylated hemoglobin, aspartate transaminase, acid phosphatase and alkaline phosphatase (Nugroho et al., 2012).

3.4. *Barleria prionit*

Extracts of the root and leaf of *Barleria prionitis* in alcoholic medium were administered to diabetic rats at a dose of 200 mg/kg for 14 days, and it was observed that it decreased the blood glucose level and glycosylated hemoglobin level. In addition, it has also been shown that the levels of liver glycogen and serum insulin have increased significantly (Dheer & Bhatnagar, 2010).

3.5. *Capparis desidua*

Extracts of *Capparis decidua* stem formed with ethanol and water were applied to diabetes model rats at a dose of 250-500 mg/kg for 21 days and it was determined that it helped reduce blood sugar levels in rats (Zia-Ul-Haq et al., 2011).

3.6. *Cassia grandis*

It has been reported that extracts of *Cassia grandis* prepared with ethanol and water, applied as a ten-day treatment, reduce blood sugar and TG levels and show antidiabetic activity (Lodha et al., 2010).

3.7. *Ceriops dekandra*

Ethanol extracts of *Ceriops decandra* leaves were administered to diabetic rats at doses of 30, 60, 120 mg/kg for 30 days, and their antidiabetic activity was investigated. It was determined that glycogen, hemoglobin, blood sugar and some enzymes involved in metabolism were regulated in the diabetic group to which the extract was administered, and when the applied dose levels were compared, it was reported that the highest antidiabetic activity was shown at 120 mg/kg (Nabeel et al., 2010).

3.8. *Colocasia esculenta*

To evaluate the anti-diabetic activity of *Colocasia esculenta*, the extract obtained with 400 mg/kg ethanol was given to rats for 14 days.

Accordingly, it has been noted that blood sugar levels were significantly reduced and body weight loss was achieved (Kumawat et al., 2010).

3.9. *Costus igneus*

In the diabetic albino rat model, ethanolic extracts of *Costus igneus* leaves significantly reduced blood sugar level and prevented body weight loss with its anti-diabetic potential (Hegde et al., 2002).

3.10. *Eucalyptus citriodora*

Aqueous extracts of *Eucalyptus citriodora* leaf were administered to diabetic rats at 250-500 mg/kg for 21 days and were found to significantly reduce blood sugar levels (Patra et al., 2009).

3.11. *Ficus bengalensis*

Aqueous extract of *Ficus bengalensis* bark was administered to insulin-dependent/non-insulin dependent diabetic rats at 1.25 g/kg for 4 weeks. Plasma glucose and serum lipid level. It shows that *F. bengalensis* has anti-diabetic potential (Gayathri & Kannabiran, 2008).

3.12. *Heinsia crinata*

Ethanolic leaf extract of *Heinsia crinata* significantly reduced fasting blood glucose levels in diabetic rats for 2 weeks (Okokon et al., 2009).

3.13. *Helicteres isora*

Butanol and aqueous ethanol extracts of *Helicteres isora* root were administered to diabetic rats at a dose of 250 mg/kg for 10 days, and their antihyperglycemic and hypolipidemic activities were investigated.

Reductions in TG, blood sugar and urea levels were seen in the group treated with extracts. More detailed histological examinations revealed that the renal glomeruli, pancreatic islets and liver returned to normal size and therefore had antidiabetic potential (Venkatesh et al., 2010).

3.14. *Ipomoea reniformis*

In diabetic rats, 300-600 mg/kg of ethanol and aqueous extracts of the sap of the *Ipomoea reniformis* plant for 12 days of treatment significantly reduced blood sugar and lipid levels. Based on the data obtained, it was found that *I. Reniformis* plant has significant antidiabetic antihyperlipidaemic potential (Bothara & Kumar Vaidya, 2016).

3.15. *Juglans regia*

Antidiabetic effects of methanolic extract of *Juglans regia* leaves were administered at 250 mg/kg and 500 mg/kg for three weeks in male wistar diabetic rats. *J. regia* significantly reduced blood sugar and TG levels. In addition, SOD increased GPX and cell antibody levels (Teymouri et al., 2010).

3.16. *Lantana aculeata*

The anti-diabetic effect of ethanolic extracts of dried mature roots of *Lantana aculeata* was evaluated in diabetic rats at doses of 25, 50 and 100 mg/kg during 30 days of treatment. When the results were examined, it was determined that this plant extract significantly reduced blood sugar levels. It has also been reported that while reducing TG level, it regulates insulin and glycogen concentration dose-dependently (Patel et al., 2012).

3.17. *Lemonia acidissima*

In diabetic rats, methanolic extract of the *Limonia acidissima* plant significantly reduced malondialdehyde (MDA) and blood sugar levels in 21 days of treatment at 200 and 400 mg/kg. In addition, the activity of enzymes such as SOD and CAT, which show the antioxidant and antidiabetic potential of the plant, was found to be higher in the treated group compared to the control group (Kerkar et al., 2020).

3.18. *Luffa aegyptiaca*

Alcoholic and aqueous extracts of *Luffa aegyptiaca* in diabetic rats for 15 days of treatment at 100 mg/kg significantly reduced blood glucose of hyperglycemic rats (Patel et al., 2012).

3.19. *Momordic charantian*

The antihyperglycemic and antioxidative properties of aqueous extracts of *Momordic charantia* pulp were investigated in diabetic rats for 30 days of treatment. The plant extract has been reported to reduce blood sugar levels (Tripathi & Chandra, 2010).

3.20. *Mukia maderaspatana*

In diabetic rats, methenolic root extract of *Mukia maderaspatana* was used at a dose of 500 mg/kg for 21 days of treatment. TG has been reported to significantly reduce phospholipids, LDL, and very low-density lipoprotein (VLDL). Additionally, it decreased serum glutamate, oxaloacetate transaminases, serum glutamate, pyruvate transaminases, and alkaline phosphatase level (Wani et al, 2011).

3.21. *Nymphaea pubescens*

Ethanolic extract of *Nymphaea pubescens* significantly reduced blood glucose levels in diabetic rats after 14 days of treatment at 200 and 400 mg/kg. More detailed histopathological analysis revealed its regenerative potential supporting antidiabetic activity (Patel et al., 2012).

3.22. *Ocimum gratissimum*

In diabetic Wister rats, methanolic extracts of *Ocimum gratissimum* showed a significant reduction in blood glucose level (500 mg/kg). Methanolic extracts of O. sanctum, *Ocimum americanum* and *Ocimum basilicum* also showed similar effects (Parasuraman et al., 2015).

3.23. *Paspalum scrobiculatum*

It was determined that aqueous and ethanolic extracts of *Paspalum scrobiculatum* reduced blood sugar levels and lipid parameters in diabetic rats at doses of 250 and 500 mg/kg as a 15-day treatment. It was reported that in the group administered high doses of the extract, the glycogen content in the liver increased significantly and there was a significant decrease in the level of glycated hemoglobin. Additionally, the 500 mg/kg level showed higher antidiabetic activity compared to the 250 mg/kg dose level (Jain et al., 2010).

3.24. *Panax ginseng* CA Meyer

Panax ginseng CA Meyer is a traditional medicinal herb that has been widely used for many years (Yun, 2015). Ginseng belongs to the Panax genus in the *Araliaceae* family (Attele et al., 2002). It is typically found in cooler climate regions such as Korea, Eastern Siberia, Northeast China, and North America. Some active substances are found in all parts of plants, including phenols, amino acids, alkaloids, polypeptides, proteins and vitamins B1 and B2. Many bioactive compounds are present on the root of the plant, such as triterpene saponins or glycosides commonly referred to as ginsenosides, vanillic acid, panaxanes and salicylates (Tran et al., 2020). The ingredients contained in Ginseng, its chemical content; Depends on geographical location, climate, extraction method (Ratan et al., 2021).

3.25. *Coriandrum sativum* L.

Coriandrum sativum L., a member of the *Apiaceae* family, known as coriander, has both medicinal and nutritional properties and is widely used (Asgarpanah, 2012; Salehi et al., 2019). It is a herbaceous plant widely grown in the Mediterranean region, North Africa, Central Europe and Asia (Laribi et al., 2015). Dried seeds of coriander are used in the food industry, medicine, perfumery and cosmetics industries. Linalool is the main component of coriander essential oil (Özyazici, 2021). Coriander essential oil contains bioactive compounds fatty acids, flavonoids, carotenoids, and coumarin (Gajera & Wadiye, 2020). However, the bioactive components of the plant are affected by many factors such as the developmental stage of the plant, geographical region, cultivation condition, processing, storage time and storage condition. Additionally, the extraction method may affect the types and amounts of bioactive compounds identified (Prachayasittikul et al., 2018).

3.26. *Zingiber officinale* Roscoe

Zingiber officinale Roscoe, known as ginger, belongs to the *Zingiberaceae* family. It is considered an important spice with health benefits, used as a spice all over the world due to its sharp and typical aroma (Zhu et al., 2018). Although it originated in southern China, it is grown in many tropical and subtropical nations, including those in East, Southeast, and South Asia (Tran et al., 2020). There are many different ingredients in ginger, depending on where they come from and whether or not they have been dried (Ali et al., 2008). In fresh ginger, volatile substances include sesquiterpene and monoterpenoid hydrocarbons, which provide ginger's distinctive aroma and taste. pungent, non-volatile compounds; gingerols, shogaols, paradols. Gingerols, a homologous family of phenols, are primarily responsible for the pungent taste of fresh ginger. Due to the shogaol, which are dehydrated forms of gingers, there is a strong pungency in dry ginger (Butt & Sultan, 2011). The composition differs according to the place of origin and whether it is fresh or dry (Ali et al., 2008). In fresh ginger, volatile substances include sesquiterpene and monoterpenoid hydrocarbons, which provide ginger's distinctive aroma and taste. Zingerone, gingerols, paradol and shagaol and are nonvolatile pungent compounds. The sharpness of fresh ginger; It originates from gingerols, a homologous series of phenols, and its dry form originates from shogaols, which are anhydrous forms of the same compound (Butt & Sultan, 2011).

3.27. *Cinnamomum verum* J. Pressl

Cinnamomum verum J. Presl, known as cinnamon, is an evergreen tree of the *Lauraceae* family (Ribeiro-Santos et al., 2017). The dried barks of cinnamon are used to flavor or spice a variety of foods and as a therapeutic agent for a variety of diseases. *Cinnamomum verum* is native to Sri Lanka and southern India but is also found in Southeast Asia, China, Burma, Indonesia, Madagascar, the Caribbean, Australia and It is also found in Africa. Essential oil contains oxygenated hydrocarbons, polyphenols and terpene groups (mono-di terpenes, sesquiterpenes). The concentration of cinnamon compounds also depends on the type of plant, cross section of the tree, and stage of maturity. These factors may affect the basic properties of cinnamon extract (Błaszczyk et al., 2021).

3.28. *Momordica charantia* L.

The *Cucurbitaceae* family includes *Momordica charantia* L., commonly referred to as bitter melon or bitter melon (Çiçek, 2022; Verma et al., 2018). It is a tropical plant grown in Asia, India, East Africa and South America. Its fruits are widely used as vegetables and in the treatment of diabetes in different parts of the world (Abascal & Yarnell, 2005; Xu et al., 2015). Triterpene, proteide, steroid, alkaloid, inorganic, lipid and phenolic compounds are the main components responsible for the antidiabetic effects of bitter melon (Joseph & Jini, 2013).

3.29. *Phyllantu emblica* L.

Phyllanthu emblica L., also called Amla or Indian Gooseberry, belongs to the Euphorbiaceae family. It is a tree native to India and Southeast Asia. The compounds found in it have been associated with antidiabetic effects. It has rich phytochemical components distributed in different parts of the plant (root, leaf, fruit) (Ahmad et al., 2021; Gul et al., 2022) Vitamins (A, C, E and K), flavonoids, polyphenols, tannins and minerals, etc. It contains various phytochemicals such as (Fatima et al., 2014). Fruit, leaves and bark contain large amounts of tannin (Ahmad et al., 2021).

4. CONCLUSION

DM is caused by absolute or relative lack of insulin secretion and insulin resistance, causing carbohydrate, fat and protein metabolism disorders. It is a disease characterized by high blood sugar levels that are responsible for high morbidity and mortality. DM causes many diseases, including kidney failure and acute-chronic complications. Recently, various pharmacological treatments have been developed in addition to diet and exercise for the treatment of diabetes. There are two treatment methods available for the treatment of DM. Exogenous insulin intake and oral hypoglycemic agents. Serious complications such as ketoacidosis and metabolic acidosis are observed in diabetes. Sedentary life, which is a problem in the modern world, contributes to the development of diabetes, which is associated with obesity. Pancreatic β-cell dysfunction, development of insulin resistance and impaired glucose tolerance can cause mitochondrial dysfunction resulting in diabetes. Experimental studies show that exposure to oxidative stress also activates stress that causes diabetes. Antidiabetic drugs used today have been described in many animal models, but they do not offer a fully equivalent treatment for diabetes. Due to the side effects of hypoglycemic agents used for diabetes, different treatment searches have emerged. For this reason, medicinal plants and their chemical components are preferred in the treatment of diabetes. Scientific and clinical studies are still needed to increase the effectiveness of plant-derived agents in modern medical practices. There is a need for validation of plant-derived drugs through biological, pharmacological and toxicological evaluations and animal models. The development and use of herbal medicines as an alternative way to treat diabetes is still of great importance today.

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CHAPTER 6

THERAPEUTIC APPROACH TO MEDICINAL PLANTS EFFECTIVE IN OBESITY AND THEIR MECHANISMS

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DOI: https://dx.doi.org/10.5281/zenodo.10454597

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INTRODUCTION

Obesity is a disease that affects public health, its prevalence continues to increase worldwide and poses a risk for many metabolic disorders. It is known that overweight individuals resort to many methods to reduce their body weight. Additional treatment options are needed to help lose weight along with exercise and healthy nutrition that will improve the quality of life. Therefore, the use of medicinal plants in obesity constitutes one of the treatment strategies. In this context, studies have been conducted on many edible plants and their components that have therapeutic effects (Sun et al., 2016). According to epidemiological studies, certain plants have been reported to have the potential to prevent obesity. The action mechanisms of medicinal plants have been evaluated through clinical studies, including in vivo and in vitro studies. Accordingly, reducing appetite, inhibiting gastrointestinal enzymes, preventing lipogenesis and adipogenesis, controlling lipid metabolism, maintaining balance by increasing energy expenditure, that is, modulating metabolism, are among the mechanisms (Karri et al., 2019). Additionally, improving inflammation caused by obesity is also among the mechanisms (Williams et al., 2017). Parallel results have been obtained between clinical trials and other studies. It is known that many edible plants, including many fruits, legumes, cruciferous vegetables and grains, have anti-obesity properties. At the same time, studies conducted with plant extracts and their various solvents have reported anti-inflammatory properties (Liu et al., 2017). For the anti-obesity properties of plants, active ingredients must be isolated. The effective and non-toxic dose must be calculated and further studies must be conducted on the molecular mechanisms. Plant extracts contain many active ingredients such as terpenes, polyphenols, alkaloids and polysaccharides. These need to be isolated and purified by various separation methods. It is important to evaluate the anti-obesity activity or synergistic effects of two or many plants. In short, plants with anti-obesity properties are promising in terms of treatment effectiveness. Extensively researching plants with medicinal effects for obesity will support this issue (de Freitas Junior and de Almeida, 2017).

1. OBESITY

Obesity is a serious public health problem that is increasing globally. This disease, also known as globesity, is characterized as an epidemic. Due to the increasing prevalence of obesity, the World Health Organization (WHO) considered obesity as an epidemic in 1997 (Koliaki et al., 2023). Obesity has been described as a multifactorial and also a chronic disease. Obesity is characterized by excessive weight gain due to an increase in adipose tissue when the energy intake is greater than the energy expended (Spiegelman and Flier, 2001). Obesity is known to be one of the main risk factors for metabolic diseases. Obesity being a risk factor depends on adipose tissue types. In particular, increased visceral adipose tissue is associated with type 2 diabetes, heart disease, non-alcoholic fatty liver disease and some cancers (Guo et al., 2018). Obesity is associated with diabetes, premature death, cardiovascular disease and many other diseases. It also reduces quality of life and endangers life (Hruby et al., 2016). At the same time, obesity has been linked to the risk of contracting viral infections. This is evidenced by individuals with obesity having an increased risk of contracting COVID-19 (Zhao et al., 2020). In general, obesity is most common in women, and socioeconomically, it is more common in certain societies and generally in people with lower education levels (Arroyo-Johnson and Mincey, 2016). Obesity affects especially women in low-income countries, but affects all age groups and genders in high-income countries. Obesity is distributed differently in societies with low socioeconomic status (Swinburn et al., 2011). Unhealthy diets and lack of movement due to the development of technology 2 billion people in the world have a high body mass. According to the World Obesity Atlas 2023 statistical data, 38% of the world has been diagnosed with obesity and body mass indexes (BMI) higher than 25 kg/m^2. According to future projections, this rate is expected to reach 51% in the future (Lobstein T, 2023). In addition, a two- to threefold increase in obesity in school-age children has been recorded in the last three decades (Wang and Lobstein, 2006). The imbalance of energy intake leads to lipid hypertrophy and hyperdifferentiation of adipocytes. This results in excessive energy storage (Hara-Chikuma et al., 2005). Abnormal changes in adipocytes lead to the production of free fatty acids, adipocytokines and inflammatory factors secreted from adipose tissue, causing systemic disorders and further triggering obesity (de Ferranti and Mozaffarian, 2008). Obesity requires a change in living conditions. Pharmacotherapy is used as the primary treatment option for obesity. However, side effects develop due to the use of synthetic drugs in obesity (Schroll et al., 2016). For example, the drug orlistat used in the treatment of obesity enzymatically helps to treat obesity and inhibits lipase. However, there are gastrointestinal side effects that adversely affect health (Sjostrom and Andersen, 1998).

2. IMPORTANCE OF MEDICINAL PLANTS IN OBESITY

Dietary supplements are products used to supplement one or more dietary components, including protein, minerals, vitamins, sports supplements and weight loss supplements (Ahmad et al., 2020). Consumption of supplements has increased and become popular around the world. Due to the increasing demand, supplements for weight loss have also become one of the top support products (Sun et al., 2016). Medicinal plants and their active components contribute to processes such as the prevention or treatment of many diseases. Because medicinal plants are non-toxic or have lower toxicity (Sun et al., 2016). Medicinal plants can be consumed as natural supplements for weight loss. Examples of medicinal herbs used for weight loss include garcinia, white beans, green tea and Yerba Maté (Barrett and Udani, 2011; Kim et al., 2015; Jayawardena et al., 2020). Plants with anti-obesity properties such as red cabbage, aloe vera, ginger, omija and blueberries are among the edible plants (Park et al., 2017; Podsedek et al., 2017; Rahoui et al., 2018; Kowalska et al. 2019; Mao et al., 2019). Active components such as quercetin, capsaicin, kaempferol, anthocyanin, and diocin found in medicinal plants have been reported to be used to reverse excess weight (Badshah et al., 2013; Poudel et al., 2014; Seo et al., 2015; Tremblay et al., 2016; Torres-Villarreal et al., 2019). The anti-obesity properties of medicinal plants occur through various mechanisms. Medicinal plants exhibit their properties by inhibiting appetite, inhibiting adipogenesis and lipogenesis, increasing energy burning, reducing the absorption of lipids and carbohydrates, regulating lipid metabolism, regulating the intestinal microbiota and improving inflammation (Muccioli et al., 2010; Poudel et al., 2014; Tung et al., 2017, Rahoui et al., 2018).

3. MECHANISMS OF MEDICINAL PLANTS ON OBESITY

3.1. Peripheral Effect Of Medicinal Plants in Obesity

Plant components with anti-obesity properties can show their effects peripherally, independently of the central nervous system. The aim is to restrict digestion and absorption and keep many pathways under control in order to reduce calories (Birari and Bhutani, 2007).

3.1.1. Inhibition of relevant enzymes

Gastrointestinal enzymes are elements that play a role in the development of obesity. Digestion and absorption of biomolecules such as lipids and carbohydrates in foods are regulated by many enzymes. (Marrelli et al., 2014; Rahman et al., 2017). Obesity can be treated by inhibiting the digestion and absorption of dietary fats and carbohydrates. Lipase can be mentioned as enzymes that digest lipids, and α-glucosidase or α-amylase can be mentioned as enzymes that digest carbohydrates (Spínola et al., 2017). Lipases and bile salts break down dietary fats into fatty acids. These are then absorbed from the small intestine, synthesized again in the body and stored in the tissue

(De La Garza et al., 2011). Enzymes such as α-glucosidase and α-amylase digest carbohydrates to form monosaccharides. Some of the monosaccharides are converted into glycogen and fat, causing excess weight (Dhital et al., 2017). Accordingly, inhibition of gastrointestinal enzymes that play a role in digestion and absorption may prevent excessive weight gain and have anti-obesity properties. It has been supported by many studies, both in vitro and in vivo, that many plants have an effect on gastrointestinal enzymes and fight obesity by modulating their activities. One of the enzymes targeted for obesity treatment is lipoprotein lipase (LPL). LPL, which plays a role in lipid metabolism, is found at high levels in overweight individuals considered obese. Obesity can be controlled by inhibition of LPL (Woollett et al., 1984)

Pancreatic lipase (PL) is an important enzyme in lipid metabolism. It takes part in the digestion of lipids by converting triglycerides into mono and diglycerides. According to supporting studies, when PL is inhibited, lipids cannot be converted into smaller forms, thus absorption decreases. It is possible to reduce the calories consumed in obese individuals and thus prevent the formation of excess weight. PL is the most studied enzyme because it is one of the effective ways to study the antiobesity properties of natural products such as plants (Birari and Bhutani, 2007). Supplement components show their effect in the intestine by tightly binding with serine in the active site of the PL enzyme. Accordingly, it cannot break down lipids into smaller units and digestion of lipids is prevented. Weight loss occurs due to decreased lipid digestion (Tsujita et al., 2006). Many plants that inhibit PL have been studied. Among these plants, *Nelumbo nucifera* (Ono et al., 2006), *Panax japonicus* (Han et al., 2005), *Platy-codi radix* (Han et al., 2000) and *Salacia reticulata* (Kishino et al., 2006) have PL inhibitory properties. Phytochemicals that inhibit PL are generally flavonoids, saponins, polyphenols or caffeine group compounds (Kim et al., 2005; Moreno et al., 2006; Shimoda et al., 2006). Additionally, studies have been conducted on tea types to prevent PL activity. For example: green tea, black tea and oolong etc. Polyphenolic compounds contained in teas strongly inhibit PL (Han et al., 1999; Nakai et al., 2005; Thielecke and Boschmann, 2009). Polymerization of galloyl and/or flavan-3-ol components found in teas causes an increase in PL inhibition (Nakai et al., 2005).

Cholesterol, as a lipid component, is a lipid that plays a role in weight gain. According to a study conducted on mice, wheat alkylresorcinols were reported to inhibit cholesterol absorption in the intestine, which would promote cholesterol excretion (Oishi et al., 2015). In a study involving mice given a high-fat diet, they were fed a milk diet derived from soy residue to measure its effectiveness. Accordingly, it was determined that soy milk given to obese mice reduced triglyceride levels in the blood and inhibited lipase in the intestine, resulting in a decrease in the digestion and absorption of lipids (Nishibori et al., 2018). The effectiveness of plants such as *Crataegus pubescens*, *Ocimum sanctum*, *Adiantum capillus-veneris*, *Leopoldia comosa*, *Cosmos caudatus Kunth* leaf and mahanimbine against obesity has been investigated in animal models and it has been reported that they reduce carbohydrate and lipid absorption (Shang et al., 2021). Inhibition of enzymes in carbohydrate metabolism is another pathway to obesity. Accordingly, total phenolic compounds and diacylated anthocyanins contained in red cabbage inhibited alpha-glucosidase. However, monoacylated and diacylated anthocyanins in red cabbage inhibited alpha-amylase (Podsedek et al., 2017). In summary, according to research, it has been proven that the inhibition of gastrointestinal enzymes by many plants is effective in obesity. Such plants are shown as potential candidates for anti-obesity. The active components of plants should be separated and which enzymes they inhibit should be studied in depth using advanced methods.

3.1.2. Inhibition of adipogenesis

Adipose tissue consists largely of white adipose tissue (WAT). This is often the case in animals and humans. WAT is a high energy source where the body's energy needs are stored in the form of triglycerides. Metabolic imbalances, that is, energy intake being higher than loss, are associated with weight gain due to an increase in WAT rate (Morton et al., 2006; Barceló-Batllori and Gomis, 2009). Triglycerides fulfil the energy requirement during prolonged fasting and energy deficiency. When we look at modern societies, it has been observed that obese individuals have a considerable increase in WAT rates (Gregoire et al., 1998). Adipocytes, where WAT is stored, increase over time in obese individuals and form additional adipocytes, resulting in an expansion of adipocytes. The anti-obesity approach focuses on the reduction in the number and size of adipocytes, also involves the reduction of adipokines and the control of related expressed signaling pathways (Rayalam et al., 2008). Adipogenesis can be defined as a process controlled by many genes within the scope of lipid metabolism and associated with the expression of these genes. The process of differentiation of adipocytes is controlled mainly by transcription factors such as sterol regulatory element binding protein (SREBP), C/EBP and peroxisome proliferator activator receptor (PPAR). Changes in PPAR-γ expression during the differentiation of adipocytes control the adipogenesis process (Spiegelman et al., 1997). It is known that the cell membrane structure consists of phospholipids. Polyunsaturated fatty acids (PUFAs) are also essential components of the cell membrane. Additionally, PUFAs are involved in adipogenesis by affecting the expression levels of certain genes in adipocytes and are a signal transducer (Lombardo and Chicco, 2006). It has been reported that compounds and flavonoids such as quercetin, catechin and kaempferol found in various plants reduce the expressions of SREBP-1, C/EBP-α and PPAR-γ, which play a role in adipogenesis. Accordingly, it has been demonstrated that these components inhibit adipocyte differentiation before it reaches an advanced stage. As a result, it was observed that fat tissue decreased. It has also been reported that catechins and epigallocatechin gallate found in tea reduce fat tissue (Kao et al., 2000; Sayama et al., 2000; Murase et al., 2002; Chien et al., 2005). Many natural compounds such as resveratrol, capsaicin, genistein, quercetin, esculetin and conjugated linoleic acids, in addition to their inhibitory properties of adipocyte proliferation, also exhibited apoptotic effects. It has been reported that these components phosphorylate the ERK1/2 pathway, activate mitochondrial signaling, induce apoptosis in adipocytes due to activation of the AMPK pathway, and show antioxidant activity (Rayalam et al., 2008). Sirtuin 1 is one of the molecules targeted in anti-obesity. Due to resveratrol-mediated reduction of adipogenesis, Sirtuin suppresses PPAR-c and promotes the transport of lipids. Accordingly, increased sirtuin expressions have been associated with anti-obesity (Picard et al., 2004; Rayalam et al., 2008).

3.1.3. Reducing appetite

Increased appetite causes energy intake imbalance, food consumption increases and obesity develops (Timper et al., 2017). One of the anti-obesity approaches is to suppress increased appetite. If appetite is controlled, more food intake than necessary is prevented and, accordingly, weight gain is reduced (Zhang et al., 2014). It is known that certain drugs or herbs have appetite suppressant properties. Thus, it helps lose weight and prevents obesity. According to an animal study, rats were given dietary fiber including beta-glucan, pectin and fructo-oligosaccharides. According to the data obtained, beta-glucan reduced the weight of rats by 10%, pectin by 19% and fructo-oligosaccharide by 17%. (Adam et al., 2014).

Fatty acid synthase (FAS), which plays a role in the synthesis of long-chain fatty acids, degrades malonyl-coA and acetyl coenzyme A. It has been suggested that obesity can be treated if FAS enzyme inhibition is achieved. According to a study, mice were given FAS inhibitors. Accordingly, it has been revealed that FAS inhibitors reduce appetite and food and also regulate weight (Loftus et al., 2000). Many herbs have been reported to act as FAS inhibitors, ultimately suppressing appetite. Epigallocatechin gallate found in green tea bound reversibly or irreversibly to FAS and inhibited this enzyme. This hemoglobin component has been reported to inhibit FAS, such as cerulenin and C57 (Wang et al., 2001).

There are many factors that regulate appetite. Among these, certain hormones and neurotransmitters control hunger and satiety (Shawky and Segar, 2018; Li et al., 2019; Tas et al., 2022). Neuropeptide Y (NPY)/agouti-related molecule located in the arcuate nucleus of the hypothalamus is responsible for increasing appetite and has orexigenic properties (Luquet et al., 2005). The neurotransmitter with anorexigenic properties in the hypothalamus is proopiomelanocortin (POMC). POMC acts on melanocortin receptors. Melanocortin receptors and alpha-melanocyte-stimulating hormone (MSH) are affected by insulin and leptin. Accordingly, food intake is controlled (Yang et al., 2022). Weight gain can be regulated by controlling the secretion of leptin, NPY and POMC in the leptin-melanocortin pathway by certain plants. On the other hand, plants can also control hunger and satiety through digestive system hormones and fat tissue. Leptin is an adipokine defined as a hormone secreted from adipocytes. Leptin controls appetite by interacting with components in the hypothalamus. In an animal experiment, when the sulforane compound found in cruciferous vegetables was given intraperitoneally to obese mice, it suppressed food intake via leptin (Shawky and Segar, 2018). Cinnamaldehyde, the phytochemical component of cinnamon, reduced ghrelin levels in the stomach. This is regulated by increasing the expression of transient receptor potential-ankyrin receptor 1. Therefore, food intake decreased with decreased ghrelin levels (Camacho et al., 2015). Studies show that edible and medicinal plants can regulate appetite with neurotransmitters that function through the hypothalamus, as well as hormones such as leptin, insulin or alpha-MSH. (Shang et al., 2021).

3.1.4. Thermogenesis

Hyperplasia of adipocytes and increased fat storage result from an imbalance in energy intake (Flatt, 2007; Redinger, 2009). The body's fat storage is generally provided by WAT. Brown adipose tissue (BAT) is adipose tissue that is found in lesser amounts. BAT releases energy as heat and functions in the process as thermogenesis (Cannon and Nedergaard, 2004). BAT controls weight gain through thermogenesis and prevents obesity. Mitochondrial miscoupling protein (UCP1) is a key protein that helps dissipate energy as heat, playing a role in thermogenesis. Controlling and treating obesity has been associated with increased *UCP1* gene expression (Kumar et al., 1999). There is evidence that activation of thermogenesis by medicinal plants is associated with reduced weight gain in obesity. In a study, it was noted that when the ethanol-containing extract obtained from the *Solanum tuberosum* plant was given to rats fed a high-fat diet, it increased the expression of UCP3 in the liver and BAT, and a decrease in fat tissue was also detected (Yoon et al., 2008). Capsaicin and caffeine have been reported to increase energy expenditure through thermogenesis (CV et al., 2012). According to a study, *UCP1* expression increased in mice given 6-paradol. This helped stimulate thermogenesis and decrease in body mass in BAT (Haratake et al., 2014). Administration of black soybean husk extract to mice increased the expression of UCP1 in BAT and UCP2 in WAT, which was associated with its anti-obesity property (Kanamoto et al., 2011). Additionally, administration of russelioside B to obese rats was associated with an increase in UCP1 expression in BAT and an increase in the expression of carnitine palmitoyltransferase-1 (CPT-1), which plays a role in β-oxidation of fatty acids, with energy expenditure. (Abdel-Sattar et al., 2018).

3.2. Central Effect of Medicinal Plants in Obesity

Obesity can be controlled by reducing energy intake. Many medicinal plants and their components can regulate appetite and suppress hunger by acting on the central nervous system.

3.2.1. Neuropeptide Signaling Regulators

Energy intake and expenditure must be in balance, in such a case body weight remains constant. However, when energy homeostasis is disrupted, weight gain is observed. (Flier, 2004; Morton et al., 2006). Hormones such as leptin, ghrelin and insulin affect the lipid stores in the body by acting on the central nervous system (Stern et al., 2016; Lv et al., 2018).

Two types of neurons located in the arcuate nucleus of the hypothalamus regulate appetite and are effective in signaling. These:

1) Anorexigenic: These neuropeptides are appetite suppressants. POMC and cocaine and amphetamine-regulated transcript (CART) are included in this group.

2) Orexigenic: These neuropeptides are appetite stimulants. agouti-related peptide (AgRP) and NPY are included in this group.

Leptin and insulin interact with receptors on the POMC neuron. POMC stimulates α-MSH by signaling, and through a series of transmissions, appetite is suppressed (Morton et al., 2014; Andermann and Lowell, 2017). In the fed state, leptin binds to its receptor on NPY/AgRP neurons and NPY is inhibited. In the fasting state, the decrease in ghrelin, leptin and insulin levels activates NPY/AgRP neurons (Jeong et al., 2017).

Appetite suppression and energy balance can be controlled by medicinal plants through the central nervous system. It has been proven by research that extracted green tea can control plasma leptin levels (Di Pierro et al., 2009). According to an animal study, adlay seed extract was given to rats fed a high-fat diet. This extract has been noted to control tumor necrosis factor-alpha (TNF-α) expressions along with leptin levels. Accordingly, appetite decreased in rats, a decrease in fat tissue was detected, and a decrease in serum lipid profile was observed (Kim et al., 2004). According to a study conducted on rats fed a high-fat diet, saponin obtained from Korean ginseng was found to be effective in preventing obesity. It has been noted that Korean ginseng saponin suppresses appetite by regulating leptin and NPY expressions (Kim et al., 2004). Accordingly, there is limited research on the appetite-inhibiting and appetite-inducing properties of medicinal plants and natural components.

3.2.2. Monoamine neurotransmitters

Body weight can be regulated by controlling appetite with hormones and a series of neurological activities. It is possible that food intake can be controlled by signaling activated through monoamine neurotransmitters such as serotonin, dopamine and histamine. Serotonin is a monoaminergic neurotransmitter that controls certain processes, including motor, sensory and behavioral. Serotonin represents a family of approximately fourteen 5-hydroxytryptamine (5-HT) receptor subtypes. It has been reported that serotonin receptors can control body mass and therefore may be an important target for obesity (Tecott et al., 1995). It has been noted that natural components of medicinal plants can reduce appetite by controlling hunger-satiety mechanisms and monoamine neurotransmitters through the central nervous system, thus being promising for obesity (Halford and Blundell, 2000; Wynne et al., 2005). Catechins such as epigallo catechin and epigallo catechin gallate found in green tea have been frequently studied for obesity. It has been previously reported that epigallo catechin gallate acts on thermogenesis. There is also evidence here that epigallo-catechin gallate controls obesity by modulating serotonin. According to an animal experiment, obese mice were given epigallocatechin gallate. This given compound has been proven to control neurotransmitters such as 5-hydroxytryptophan and dopamine. Additionally, in the same study, it was noted that epigallocatechin gallate also has anti-inflammatory properties, and it was suggested that obesity could be alleviated through such mechanisms (Zhou et al., 2023). Hydroxycitric acid (HCA) obtained from *Garcinia cambosia* has an appetite reducing effect. It exerts its appetite-reducing effect by inhibiting the adenosine 5-triphosphate-citrate lyase enzyme. Therefore, fatty acid synthesis is suppressed. It has also been suggested that HCA induces gluconeogenesis and suppresses appetite. It has also been reported that HCA regulates food intake by affecting 5-HT and sorotonin (Ghosh, 2009).

4. EFFECT OF MEDICINAL PLANTS ON OBESITY-RELATED INFLAMMATION

Obesity causes an increase in inflammatory agents through various mechanisms. Chronic inflammation develops due to the increase in immune cells in the fat tissue (Cao Citation, 2014). Some plants have the ability to reduce inflammation that develops in obesity. Reducing inflammation, which is effective in the development and progression of obesity, can alleviate obesity (Cao, 2014). Celastrol, a natural ingredient, demonstrated its anti-obesity property by inhibiting mitogen-activated protein kinases (MAPK) such as p38, Jun N-terminal kinase (JNK) and ERK1/2. Celastrol suppresses the nuclear translocation of nuclear factor-κB (NF-κB), additionally reducing the expression of heme oxygenase-1 and nuclear factor-related factor-2. Accordingly, inflammation is prevented in obesity (Luo et al., 2017). It has been reported that quercetin reduces inflammation that develops in obesity. Signaling of MAPK and monocyte chemotactic protein-1

(MCP-1) was suppressed by quercetin in adipose tissue. Additionally, quercetin suppressed inflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-α and induced anti-inflammatory cytokines such as IL-10 (Seo et al., 2015). Medicinal plants that exhibit anti-obesity properties as anti-inflammatory also include ginger, raspberry and *Psacalium decompositum*. (Kim et al., 2018; Zhao et al., 2018). In summary, it is understood that various plants that can be considered medicinal reveal their anti-obesity properties by preventing inflammation that develops in obesity.

5. MEDICINAL PLANTS IN CLINICAL TRIALS IN OBESITY

According to experimental and epidemiological studies, it has been proven by clinical studies that many plants are effective on obesity and help recovery. In the study involving 17 obese volunteers, 900 mg of the polyphenolic Fiit-ns component was given. In line with the data, it was reported that individuals' weight decreased and their metabolic factors improved (Cases et al., 2015). In the study involving 30 obese participants, Yerba Maté capsules were given to the participants for 12 weeks, and as a result, weight loss and a decrease in waist-hip measurements were observed (Kim et al., 2015). According to another clinical study, *Fraxinus excelsior L.* seed/fruit extract was given to 22 obese participants for 3 weeks, and weight loss was recorded in the patients due to a decrease in the adiponectin/leptin ratio (Zulet et al., 2014). In another study, encapsulated vegetable and fruit juices were administered to 56 obese participants for 8 weeks. Accordingly, it was determined that obesity-induced inflammation decreased and lipid profiles decreased. At the same time, an increase in the expression of genes involved in AMP-activated protein kinase (AMPK) and NF-κB signaling was observed (Williams et al., 2017). In a study on 7 overweight women, patients were given 4 g of *Ephedra sinica* extract for 8 weeks. At the end of the study, a decrease in fat tissue was observed in the patients (Kim et al., 2014). In general, several foods and medicinal products have been used in the clinic and have been shown to have positive effects on the prevention and management of obesity. Clinical trials should confirm the effects of more plants on obesity in the future. In particular, it is essential to further investigate the safe dose and side effects of plants.

6. WHY SHOULD OBESE INDIVIDUALS PREFER HERBAL PRODUCTS?

a) Medicinal plants are 100% natural, edible ones are also available and safe

b) Can be taken without consulting any specialist

c) Availability without prescription

d) Generally does not cause side effects

e) It is an easier way to lose weight instead of exercise and dieting (CV et al., 2012).

7. FEATURES THAT A PLANT SHOULD HAVE FOR OBESITY TREATMENT

The use of herbal products is an effective option in the treatment of obesity. Overweight people in developing and developed countries need herbal products to help them lose weight. In the sections above, studies on many plants to overcome the problem of excess weight are given. However, anti-obesity studies on plants should be developed and their effectiveness should be further tested. For a plant to be an effective treatment option for obesity, it must include the following features.

a) In placebo-controlled randomized clinical trials, one herb should reduce obesity by 10%.

b) Sufficient evidence must be provided about which component of the plant is evaluated and its mechanism on obesity.

c) Other complications of obesity must also be shown to improve.

d) The active compound of the plant should be well defined and standardized.

e) There should be no side effects that will negatively affect the treatment. (CV et al., 2012).

8. CONCLUSION

Herbs and herbal compounds are an effective treatment option for obesity. According to many studies, it has been reported that the effectiveness of many plants in obesity has been tested. Treatment mechanisms include induction of thermogenesis, reduction of lipid production, increase of lipid degradation, suppression of appetite, and control of absorption-related processes. Treating obesity safely can be achieved with herbal products. Physicians also give recommendations for consuming herbal products. In addition to exercise and healthy nutrition that will improve the quality of life, consuming herbal products will be effective in alleviating obesity. For this, it is necessary to conduct studies on new plants that can significantly treat obesity.

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CHAPTER 7

THE ROLE OF MEDICINAL PLANTS IN TREATING NEURODEGENERATIVE DISEASES

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DOI: https://dx.doi.org/10.5281/zenodo.10454599

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INTRODUCTION

Pharmacological treatments currently available for neurodegenerative diseases only alleviate symptoms or slow disease progression (Rafii & Aisen, 2009; Durães et al., 2018). However, their regular use is associated with serious side effects, including toxicity, addiction, neuro-inflammation, and higher dosage regimens, which can worsen the diagnosis and impair brain function (Salawu et al., 2010). New approaches are necessary to target medicinal plants and phytochemicals with a low long-term side effect profile (Singhal et al., 2012; Lalotra & Vaghela, 2019). It is crucial to identify the appropriate molecular mechanism for targeted therapy of neurodegenerative diseases and to investigate commonly used medicinal plants and phytochemicals that may be beneficial in treating these diseases (Pohl & Lin, 2018). Due to the diversity of pathogenic mechanisms, the discovery and development of combination therapies or multitargeted drugs offer new opportunities for the healing of neurodegenerative ilnesses. There is an increasing emphasis on natural medicines with multi-component, multi-target properties and efficacy (Milke et al., 2018; Yan et al., 2022). Plants are a good source of multi-targeted compounds (Yun et al., 2012). In recent years, many studies have reported that phytochemicals and their bioactive compounds may serve as potential neuroprotective agents with protective effects against neurodegenerative diseases (Mohd Sairazi & Sirajudeen, 2020).

1. BIOACTIVE COMPOUNDS

Plants produce bioactive compounds as secondary metabolites (Bernhoft, 2010). According to Croteau et al. (2000) these compounds were classified into three main groups: phenolic compounds, alkaloids, terpenes and terpenoids (Croteau et al., 2000). Additionally, there are classes of nitrogen-containing and organosulfur compounds (Jha & Sit, 2022). Terpenes and terpenoids are obtained by combining five-carbon isoprene units. While terpenoids (isoprenoids) have oxidizable functional groups, terpenes, classified according to the number of isoprene units they contain, are entirely hydrocarbon compounds (Gershenzon & Dudareva, 2007; Tholl, 2015). Terpenes classified as monoterpenes, sesquiterpenes and diterpenes, triterpenes, tetraterpenes and polyterpenes contain 10, 15, 20, 30, 40, > 40 Carbon, respectively (Liao et al., 2016). Studies have shown that these compounds have various health benefits, such as anti-tumor, anti-inflammatory, antibacterial, antiviral, prevention and treatment of cardiovascular disease, blood glucose lowering, immunomodulatory, antioxidant, anti-aging, and neuroprotective effects (Yang et al., 2020). Alkaloids are naturally occurring metabolites that contain nitrogen in their chemical structure. They have a high biological potential due to the unique arrangement of atoms (Bhambhani et al., 2021). Alkaloids are produced in both the plant and animal kingdoms through the combination and arrangement of functional groups. This broad class of compounds is classified based on their biosynthesis pathways in plants, chemical structures, and taxonomic groups (Dey et al., 2020). Alkaloids are formed through specific chemical reactions from similar biochemical precursors. For example, L-aspartate is a precursor for pyridine and pyridinone type alkaloids (Lichman, 2021). Depending on the binding site of the nitrogen atom in their structure, alkaloids are classified as heterocyclic and non-heterocyclic compounds. In heterocyclic alkaloids synthesized from compounds such as L-tyrosine, L-phenylalanine, L-ornithine, L-tryptophan, L-lysine and L-histidine, the nitrogen atom is located in the main heterocyclic ring, while in non-heterocyclic alkaloids such as phenylethylamine, ephedrine, capsaicin, colchicine and paclitaxel, the nitrogen atom is located in the aliphatic chain outside the cyclic ring (Bhambhani et al., 2021). Alkaloids synthesized by plant species of the identical genus are classified in a same category. For example, Opium alkaloids, such as codeine, morphine, thebaine, noscapine, and papaverine, are the five primary alkaloids found in the raw poppy plant (Beaudoin & Facchini, 2014). Alkaloids have been reported to have neuroprotective properties such as lowering oxidative stress, Declining neuroinflammation, inhibiting cholinesterases and apoptosis, and regulating autophagy (Ali et al., 2023). They have also been found to have antimicrobial, antifungal, and antiviral effects (Ettefagh et al., 2011; Yohannes et al., 2018; Thawabteh et al., 2019). Phenolic compounds are organic compounds that serve as secondary metabolites in plants They consist of compounds containing at least one aromatic ring attached to at least one hydroxyl group. Phenolic compounds can exist in free form or bound to lipids, carbohydrates, amines, cell wall components, and organic acids. (Balasundram et al., 2006; Shah et al., 2018; Arruda et al., 2019).

This class of compounds includes subcategory such as isoflavonoids, phenolic acids, flavonoids, biflavonoids, anthocyanins, lignans, tannins, and stilbenes. They have been shown to play a positive role against tumors, ulcers, allergies, platelet aggregation and cardiovascular diseases, and may decrease cancer's risk (Block, 1992; Hertog et al., 1993; Bingham et al., 2003; Alara et al., 2021). There is increasing evidence that diets high in phenols may help decrease the risk of age-related diseases, such as neurodegenerative and metabolic disorders (Castro-Barquero et al., 2020; Holland et al., 2020).

2. IMPORTANCE OF CERTAIN MEDICINAL PLANTS USED IN NEURODEGENERATIVE DISEASES

2.1. *Withania somnifera (ashwagandha)*

Withania somnifera (L.) *(Indian Winter Cherry or Indian Ginseng)* is a small, woody shrub belonging to the Solanaceae family in the plant kingdom. This plant species is found in a wide range of regions, including the Canary Islands, the Mediterranean, tropical regions of South Asian countries like Sri Lanka and India, as well as China, some Middle Eastern countries, and Africa (Ziauddin et al., 1996). Its extract contains a variety of bioactive compounds, including flavonoids, alkaloids, steroids, steroidal lactones, salts, and nitrogen-containing compounds (Dar et al., 2015). According to Sandhir and Sood (2017), these active compounds have various positive effects on the nervous, endocrine and cardiovascular systems, such as anti-inflammatory, anti-cancer, anti-stress, immunomodulatory and adaptive effects (Sandhir & Sood, 2017).

2.2 *Curcuma longa*

Turmeric, also known as *Curcuma longa*, is a perennial herb from the Zingiberaceae family that grows in Southeast Asia (Prasad & Aggarwal, 2011). It contains polyphenols, organic acids, and flavonoids, which make it useful in treating various diseases worldwide. The main bioactive compounds in turmeric are curcuminoids, including curcumin, bisdemethoxycurcumin, and desmethoxycurcumin. Turmeric has been reported to have neuroprotective, anti-proliferative, anti-inflammatory, anti-cancer, anti-diabetic, hypocholesterolemic, anti-microbial, anti-viral, and antioxidant effects (Kim & Clifton, 2018; Mehla et al., 2020; Bássoli et al., 2023).

2.3. *Panax ginseng*

Panax ginseng, a long-lived plant, is a member of the Araliaceae family (Helms, 2004). Although its homeland is Korea and China, it can also be widely grown in other countries such as Russia, Japan, Canada and the United States (Chang-Xiao & Pei-Gen, 1992; Wang et al., 2010). Throughout history, people in East Asian countries like Japan, China, and Korea have used it as medicine (Hong et al., 2013). Ginseng contains several functional components, including ginseng saponins/ginsenosides, phenolic compounds, polyacetylenes, alkaloids, sesquiterpenes, oligopeptides, and polysaccharides (Kim et al., 2018). These active ingredients have been indicated to provide several therapeutic benefits, such as adaptogenic, immunomodulatory, anti-inflammatory, antioxidant, anti-aging, anti-cancer, and anti-diabetic effects (Cho, 2012; Xie et al., 2005). Furthermore, various studies on neurological disease models have demonstrated that it possesses anti-stress, antidepressant, and neuroprotective properties (Liao et al., 2002; Kim et al., 2011; Chen et al., 2016; Im et al., 2016; Hwang et al., 2017).

2.4. *Ginkgo biloba*

Ginkgo biloba, the only surviving member of the Ginkgo family, is the oldest tree species in the world (Singh et al., 2019). It grows in China, Japan, Europe, and North America (Nakanishi, 2005). The leaves and seeds of the ginkgo tree have been used for medicinal purposes in the past. The extract of its leaves, which contains terpenoids, flavonoids, and organic acids (Shi et al., 2009; Smith et al., 1996), is the active compound known for its medicinal value. The leaves of this plant contain active components with antioxidant, radical scavenging, wound healing, and neuroprotective properties against neurodegenerative disorders (Bairy, 2002; Nakanishi, 2005; Srivastav et al., 2017; Yuan et al., 2017).

2.5. *Bacopa monnieri*

Bacopa monnieri belongs to the Scrophulariaceae family and is a plant that grows in warm, swampy wetlands in India, East Asia, Australia, and the United States. It is a medicinal herb defined in Ayurveda, the conventional medicine of India, and is considered a 'medhya rasayana', a plant that enhances cognitive function and intelligence (Nemetchek et al., 2017; Singh et al., 2020). This is primarily because of the presence of saponins known as 'bacosides'. These are complex mixtures of alkaloids, glycosides, flavonoids, and structurally similar compounds, such as pseudojujubogenin or jujubogenin glycosides (Dowell et al., 2015; Charoenphon et al., 2016).

2.6. *Crocus sativus*

Crocus sativus, also known as saffron, is a small long-lived that is a member of the Iridaceae family. It is grown in several countries, including Iran, Afghanistan, Türkiye, and Spain (Abdullaev, 1993). Saffron contains terpenoids, anthraquinones, amino acids, and alkaloids (Valle García-Rodríguez et al., 2014). Saffron has pharmacological effects that can be used to prevent and treat neurodegenerative diseases. These effects include inhibition of atherosclerosis and platelet aggregation, reduction of blood lipids, antioxidant properties, amelioration of myocardial ischemia and hypoxia, anti-inflammatory, anti-cancer, and anti-depressant functions (Poma et al., 2012; Thushara et al., 2013; Hatziagapiou & Lambrou, 2018; Rahmani et al., 2019; Zhang et al., 2019; Xue et al., 2020; Lambrianidou et al., 2021; Siddiqui et al., 2022; Singh et al., 2022).

2.7. *Allium sativum L.*

Allium sativum (garlic), is an aromatic herbaceous plant belonging to the Alliaceae family. It is consumed worldwide as food and traditional medicine for various diseases (Rivlin, 2001; Batiha et al., 2020) due to its active components (Chung, 2006). Garlic's bioactive components are classified into two categories: volatile and non-volatile. While non-volatile substances include saponins, sapogenins, flavonoids and phenolic compounds, volatile substances include thiosulfinates and organosulfur compounds (Lanzotti, 2006). These bioactive compounds have curative effects, such as being antioxidants, cardioprotective, anti-inflammatory, anticancer, antimicrobial, and immunomodulatory agents (Ashfaq et al., 2021; Nadeem et al., 2022).

2.8. *Rosmarinus officinalis*

Rosmarinus officinalis, belonging to the Lamiaceae family, is a perennial, evergreen shrub with a long lifespan. Originating from the Mediterranean region, this herb is extensively cultivated across the globe (Hamidpour, 2017). It has been used for centuries as a source of traditional medicine and it exhibits hepatoprotective, antispasmodic, anticarcinogenic, antitumorogenic, antimicrobial, anti-inflammatory, and antioxidant properties (Al-Sereiti et al., 1999). Additionally, it shows anti-diabetic and neuroprotective activities (Faixová & Faix, 2008). It contains terpenoids, essential oils, alkaloids, and flavonoids (Rahbardar & Hosseinzadeh, 2020).

3. NEURODEGENERATIVE DISEASES AND HERBAL TREATMENT APPROACH

Neurodegenerative diseases are diverse neurological disorders affecting the central or peripheral nervous system. They are marked by gradual deterioration and dysfunction of neurons or nerve cells, resulting in progressive damage. The degradation of proteins is attributed to various factors, including environmental influences, mitochondrial defects, oxidative stress, family history, and abnormal protein accumulation in neurons, etc. (Barnham et al., 2004; Beal, 2005; Brown et al., 2005; Rubinsztein, 2006; Mosconi et al., 2007). Notably, aging is considered a crucial factor in the neurodegenerative diseases (Hung et al., 2010). Prominent examples of these disorders encompass Parkinson's disease (PD), Huntington's disease (HD), Multiple sclerosis (MS), Alzheimer's disease (AD), and Amyotrophic lateral sclerosis (ALS) (Ayeni et al., 2022; Pilipović et al., 2023).

3.1. Parkinson's Disease

Parkinson's disease is a chronic and progressive disorder characterized by the gradual loss of both motor and non-motor functions (Chaudhuri & Schapira, 2009). The key pathological feature is the emergence of intracytoplasmic remnants containing alpha-synuclein aggregates, a result of the gradual loss of dopaminergic neurons in the substantia nigra and other brain structures, known as Lewy bodies. PD is characterized by a movement disorder resulting from the gradual loss of nigrostriatal neurons that use dopamine (DA) to communicate with other cells in the basal ganglia. While changes may occur in other parts of the brain (Jankovic, 2008), the depletion of these neurons is considered the primary cause of the disorder. The development of classical motor symptoms in PD, such as rigidity, bradykinesia, and tremor, is primarily caused by the depletion of dopamine from synaptic terminals in various regions of the basal ganglia. Non-motor symptoms, such as hyposmia, sleep disturbances, and depression, are frequently associated with motor symptoms (Chaudhuri & Schapira, 2009). Early occurrences of non-motor symptoms, such as depression or hyposmia, may indicate the preclinical stages of Parkinson's prior to the initiation of motor symptoms (Nilsson et al., 2001; Chaudhuri et al., 2011). In the last years, researchers have investigated the potential of natural products and plants in intervening with the mechanisms of PD development. Some plants have been shown to be more effective and reliable than conventional synthetic drugs. Studies suggest that certain natural and synthetic products may help restore mitochondrial function, alleviate oxidative stress, and exhibit neuroprotective and anti-apoptotic effects. *Ginkgo biloba*, *Curcuma longa*, *Bacopa monnieri*, and *Withania somnifera* are among the plants that have been studied for their potential in a new reparative approach to PD. In a study, researchers intraperitoneally injected rotenone to create a PD model in mice. The study reported a decrease in glutamine reductase and glutamate dehydrogenase activities and an rise in glutaminase levels. Therefore, treatment with *Bacopa monnieri* was found to have effects similar to levodopa (Hung et al., 2016). Baicalein, extracted from *Scutellaria baicalensis* roots, exhibited bioactive properties in mice induced with PD, including weakening alpha-synuclein aggregation, inducing autophagy, inhibiting apoptosis, reducing inflammation, and restoring dopamine (Kim et al., 2012). Studies suggest that curcumin, a compound derived from ginger roots, may reduce the risk of Parkinson's disease because of its anti-apoptotic, anti-inflammatory effects, and its ability to enhance antioxidant defense (Ji & Shen, 2014; Ono & Yamada, 2006; P. K. Singh et al., 2013). Ono and Yamada (2006) reported that curcumin exhibits antifibrillogenic activity and eliminates pre-formed fibrils by preventing alpha-syn fibril formation

(Morshedi et al., 2015). Cuminaldehyde, a phytochemical compound isolated from *Cuminum cyminum*, *Artemisia salsoloides*, and *Aegle marmelos*, has been found to significantly prevent alpha-syn fibrillation. Although it has much less disintegrative effect compared to pre-formed fibrils (Šneideris et al., 2015), it still shows promising results. Epigallocatechin 3-gallate (EGCG), extracted from *Camellia sinensis*, has been reported to reduce alpha-synuclein accumulation and fibrillation. This is achieved by concentration-dependent fragmentation of large alpha-synuclein fibrils into non-toxic fragments. (Ehrnhoefer et al., 2008; Xu et al., 2017). Furthermore, *Albizia adianthifolia* extract has been found to improve neurological abnormalities associated with Parkinson's disease due to its antioxidant properties. The main compound in this extract, apigenin, promotes neuronal differentiation by stimulating neurogenesis both in vitro and in vivo (Singsai et al., 2015). Singsai et al. (2015) found that *Streblus asper*, a traditional Indian herb, has neuroprotective properties and can reverse motor and social recognition deficits in a mouse model of PD. It has also been found that the caffeine in Arabica coffee has a positive effect on the symptoms of PD. For example, it reversed motor dysfunction, improved motor function, was effective against the loss of dopaminergic neurons, and reduced apomorphine-induced blood flow (Kim et al., 2001; Chen et al., 2002; Aguiar et al., 2006). S-allyl cysteine from *Allium sativum* has been shown to improve motor function by increasing dopamine levels. However, it also increases lipid peroxidation and superoxide formation. On the other hand, it increases superoxide dismutase (SOD) activity (An & Cheng, 2007; Rojas et al., 2011). Phytochemicals such as routine, catechin, and epicatechin extracted from *Chaenomeles speciosa*, a medicinal plant, effectively preserve not only cell viability and tyrosine hydroxylase (TH) activity but also behavioral performance observed in induced neurotoxic models of Parkinson's disease (Kim et al., 2010).

3.2. Alzheimer's Disease

Alzheimer's disease is a progressive, chronic neurodegenerative disease with symptoms such as memory impairment, cognitive dysfunction, and behavioral changes. Two main neuropathological features define Alzheimer's disease: the formation and accumulation of extracellular amyloid-beta plaques and the accumulation of intracellular hyperphosphorylated tau proteins, known as neurofibrillary tangles. (Apostolova, 2016). The condition's first feature involves senile plaques, which are characterized by the extracellular accumulation of the peptide amyloid-beta (Aβ). Aβ is synthesized as a result of the breakdown of Aβ precursors at the 21q21-22 genetic locus and accumulates abnormally both inside cells and in blood vessels. The second feature is neurofibrillary tangles, which are dense abnormal bundles of altered forms of microtubule-associated protein found in the cytoplasm of neurons. The brains of Alzheimer's patients exhibit several prominent pathological findings, as reported by (Hoyer, 1992; Iqbal et al., 2005; Kuljis, 2007; Fernandez et al., 2008; Bamburg & Bloom, 2009). FDA-approved drugs for Alzheimer's disease include acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and glutamate receptor antagonists (memantine), which affect neurotransmission processes. These drugs aim to minimize or alleviate the symptoms of the disease. Additionally, Aducanumab (Aduhelm), which has recently been approved by the FDA, has shown positive effects on cognitive and motor functions in Alzheimer's patients when used as an intravenous (IV) infusion therapy containing anti-amyloid antibodies. This suggests that it could potentially delay clinical degeneration. However, treatments for Alzheimer's disease often have side effects, including headaches, nausea, confusion, dizziness, falls, and amyloid-related imaging abnormalities. As a result, there is increasing interest in natural sources for discovering new and safe therapeutic agents. In this context, several studies have reported on plants and bioactive compounds that can inhibit the formation of Alzheimer's disease, cholinesterase activity, aggregation of tau proteins, and free radical formation (Murray et al., 2013; Witter et al., 2018; Armand et al., 2019; Cui et al., 2020). Herbs such as turmeric, ginseng, German chamomile, licorice root and white willow bark may play a positive role in reducing inflammation in brain tissue, thanks to their anti-inflammatory properties. *Bacopa monnieri* is a plant cultivated in South and Southeast Asia that has gained popularity for its memory-enhancing properties. Clinical studies have reported on the effects of *B. monnieri* on memory loss in individuals of different age groups (Aguiar & Borowski, 2013; Kongkeaw et al., 2014) Researches have shown that the plant's ethanolic extract inhibits acetylcholinesterase, which prevents the breakdown of acetylcholine in rat brain parts (Ahirwar et al., 2012; Le et al., 2013). Studies in rates have shown that *B. monnieri* has neuroprotective properties on cholinergic and glutamatergic signaling (Holcomb et al., 2006). Additionally, *B. monnieri* has been observed to display neuroprotective activities by reducing β-amyloid accumulation in mouse brains and limiting the toxic effects of β-amyloid in prefrontal cortex neural cells (Limpeanchob et al., 2008; Brimson et al., 2020). Other studies have shown that dichloromethane and hexane extract of this herb have protective effects against glutamate-induced toxicity in HT-22 cells and can extend lifespan. The plant also has antioxidative and ER stress-protective effects caused by mitochondrial damage (Wang et al., 2016). Researchers have reported that this plant possesses neuroprotective, anticancer, antiapoptotic, and cardioprotective properties (Blainski et al., 2013; Liu et al., 2014; Choubey et al., 2018). Resveratrol, a natural compound extracted from *Vitis vinifera*, has been proven to stabilize the structure of a-syn and prevent alpha-synuclein (a-syn) fibril formation (Caruana et al., 2016). It also reduces oxidative stress, induces mitochondrial dysfunction, promotes apoptosis, and stimulates autophagy (Wu et al., 2011; Rasheed et al., 2016;). Wu et al (2011) found that resveratrol could increase alpha-synuclein degradation in alpha-synuclein-expressing PC12 cells. The induction of the AMP-activated protein kinase (AMPK) signaling mechanism mediates this effect (Beppe et al., 2014).

3.3. Huntington's Disease

Huntington's disease, which has symptoms such as unwanted choreatic movements, behavioral and psychiatric disorders, and dementia, is defined as an autosomal dominant neurodegenerative disease of the central nervous system (Roos, 2010). The disease is caused by the presence of long repetitions of cytosine, adenine, and guanine (CAG) trinucleotides on the short arm of chromosome 4p16.3 in the Huntingtin gene (MacDonald et al., 1993). HD progresses slowly and affects various brain regions, with distinct indications. HD is a neurological condition caused by an abnormal elongation of the repeated CAG triplet sequence in the Huntington gene on the 4th chromosome. The formation and abnormal elongation of a protein containing a polyglutamine sequence poisons brain cells and leads to their death. Because HD is an inherited disease, each child of an affected parent has a 50% chance of developing the disease. (Folstein, 1989). Although the exact function of Huntington's disease is not yet fully understood, it is well-known that the polyglutamine sequence it contains is toxic to brain cells, resulting in their death. Some neurons are more susceptible to damage in Huntington's disease, as observed in other polyglutamine expansion disorders. HD is a condition that affects motor, emotional, and cognitive abilities (Brandt & Butters, 1986). Symptoms typically appear between the ages of 35 and 50, but can occur at any age from infancy to advanced age. Some patients may experience severe motor impairments along with certain dementias, and cognitive difficulties progress at a similar rate for both conditions (Brandt et al., 1988). Patients with Huntington's disease may face rehabilitation challenges rather than memory preservation, similar to conditions such as Alzheimer's. Therefore, HD has been classified as subcortical dementia (Mahdy et al., 2011). Cognitive losses accumulate gradually and can result in deficiencies in visual-spatial skills in later stages. Patients may also exhibit irritability and aggression. Currently, there is no treatment or intervention that can prevent, delay, or alter the progression of this disease. Research suggests that certain plants may enhance memory. One study found that the extract of *Ginkgo biloba* leaf has neuroprotective effects against neurodegenerative illnesses and can improve neurobehavioral deficiencies induced by 3-NP. The study discovered that EGb 761, a standard extract of G. biloba, reduced striatal MDA levels and regulated the expression levels of striatal glyceraldehyde 3-phosphate dehydrogenase and Bcl-xl. Histopathological studies supported these findings, demonstrating the neuroprotective effects of EGb 761 in HD. (Kumar & Kumar, 2009). The root extract of *W. somnifera* has been reported to enhance cognitive function, restore the activity of the acetylcholinesterase enzyme, and maintain the levels of the glutathione enzyme system in animals treated with 3-NP (Kumar et al., 2007; Kumar & Kumar, 2010). Additionally, its GABAergic and antioxidant effects have demonstrated neuroprotective effects against neurotoxicity induced by 3-NP in experimental rats (Kumar & Kumar, 2009). Research has shown that curcumin can improve body weight, reverse motor deficiencies, and increase SDH activity in rats treated with 3-NP. These findings suggest that curcumin may be a beneficial treatment for HD by improving motor and antioxidant properties, as well as cognitive dysfunction caused by 3-NP (Wu et al., 2009). Ginsenosides present in ginseng root have neuroprotective effects by inhibiting glutamate-induced calcium ion responses in neuronal cultures (Shinomol & Muralidhara, 2008). *Centella asiatica* can help increase the levels of endogenous antioxidants, such as GSH and total thiols in the striatum. This can alleviate the decrease caused by 3-NP (Allison et al., 2001). *Centella asiatica*'s activities may provide protection against mitochondrial function disorders caused by 3-NP, including decreased SDH activities, electron transport chain enzyme levels, and mitochondrial viability. These findings indicate that *C. asiatica* could be beneficial for disorders related to HD. Additionally, *Celastrus regelii* and *Tripterygium wilfordii* exhibit antioxidant (Kim et al., 2009), anti-inflammatory (Lee et al., 2011), and anticancer activities (Cleren et al., 2005). It has been found that these plants play an effective role in preventing the formation of pro-inflammatory cytokines, inducible nitric oxide synthase and lipid peroxidation. Furthermore, they protect against striatal damage caused by 3-NP by regulating heat shock protein (hsp) gene expression in dopaminergic neurons (Zhang & Sarge, 2007). These findings suggest that these plants have potential as a therapeutic agent for improving HD. Sesamol, which has been shown to reduce cellular and biochemical changes similar to those caused by 3-NP in rodents, is produced by *Sesamum indicum* (Hsu et al., 2008). Sesamol has also been shown to prevent 3-NP-induced memory impairment, neuroinflammation and oxidative stress, while enhancing synaptic plasticity associated with HD (Lefebvre et al., 1995).

3.4. Multiple Sclerosis Disease

Multiple sclerosis, a chronic autoimmune disease of the central nervous system, is characterized in its early stages by inflammation, demyelination and axonal loss (Oh et al., 2018). The course of MS varies significantly among patients. The characteristic pathological feature of the disease is demyelinating plaques that lead to perivenular inflammatory lesions. T lymphocytes, dominated by MHC class I-restricted CD8+ T cells, are involved in the inflammatory infiltrates. In addition, there are few B cells and plasma cells. Demyelination occurs due to inflammation-induced damage to oligodendrocytes. Axons are typically preserved in the early stages of the disease. However, as the disease progresses, irreversible axonal damage occurs (Trapp et al., 1998; Lassmann, 2013; Karussis, 2014). MS is a neuroinflammatory illness characterized by relapsing-remitting demyelination and is considered to be autoimmune-based (Khorramdelazad et al., 2016; Noroozi Karimabad et al., 2017). The immune system is believed to play a role in the development of the disease through the modulation of inflammation and oxidative pathways (Vazirinejad et al., 2014a). In the Experimental autoimmune encephalomyelitis (EAE) model, which is considered a well-established animal model of MS, demyelinating lesions and inflammatory reactions are clearly observed, and cognitive disorders also occur (Ayoobi et al., 2013; Fatemi et al., 2016a; Fatemi, et al., 2016b; Hollinger et al., 2016). Research has demonstrated that alternative or complementary treatment protocols, such as herbal medicines, can improve the effectiveness of current treatments for MS (Jafarzadeh et al., 2014; Jafarzadeh et al., 2015a). In a recent study, male C57BL/6 mice with EAE-induced MS showed reduced inflammatory responses and demyelinating lesions following oral administration of aqueous *Achillea* extract at doses of 40, 200, and 400 mg/kg (Vazirinejad et al., 2014b). In their study, Hendriks et al. (2004)

found that administering luteolin (100 mg/kg) orally and intraperitoneally had a suppressive effect on behavioral disorders, prevented relapses, and reduced inflammation and axonal damage in the Lewis rat model of EAE. In a recent study, it was reported that luteolin (10 μM) can enhance the maturation of oligodendrocyte progenitor cells (OPCs) in tissue culture, which are cells that produce the myelin sheath around neurons in the mouse model of EAE (Barbierato et al., 2015). However, a different study found that oral luteolin (10 mg) did not reduce disease severity in EAE female SJL/J mice. Instead, it delayed the improvement of behavioral disorders (Verbeek et al., 2005). Further research is needed to clarify the effect of luteolin in mitigating MS-related damage. Regarding apigenin, two mouse models of MS (female SJL/J and C57/BL/6 mice) showed reduced progression and relapse after oral or intraperitoneal (IP) administration of apigenin (40 mg/kg body weight) which modulated the immune system (Ginwala et al., 2016). Anxiety disorders are frequently associated with other neurological disorders, like MS, leading to debilitating conditions (Association, 2003). *Achillea* and its flavonoid components have been reported to have sedative effects. For instance, a study on Wistar rats showed that intraperitoneal injection of *Achillea* extract (100 mg/kg) had more anxiolytic and sedative effects than diazepam (2 mg/kg) (Rezaie & Ahmadizadeh, 2013). Similarly, a study on albino Swiss male mice found that chronic gavage (300-600 mg/kg) (Baretta et al., 2012) or intraperitoneal injection of *Achillea* extract (8, 10, or 12.0 mg/kg) had anti-anxiety effects (Molina-Hernandez et al., 2004).

4. CONCLUSION

This study sheds light on the potential use of medicinal plants and natural phytochemicals in treating neurodegenerative diseases closely related to oxidative stress, which can lead to apoptosis and nerve cell death. It also highlights the potential protective effects of medicinal plants against these processes, such as antioxidants and anti-inflammatories, and suggests that they may be a promising therapeutic option in the treatment of neurodegenerative diseases. Therefore, in order to make the best use of these plants and the phytochemicals they contain, future studies are required to reveal their biological mechanisms and mechanisms of action and to precisely determine their effective doses.

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CHAPTER 8

BIOLOGICAL FUNCTIONS OF ESSENTIAL OILS OBTAINED FROM MEDICINAL PLANTS AND THEIR EFFECTS ON THE LUNG

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DOI: https://dx.doi.org/10.5281/zenodo.10454601

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INTRODUCTION

Medicinal aromatic plants have many biological activities in terms of health. Non-herbal and synthetic drugs used in the treatment of diseases have many side effects. Plants are an effective strategy in the treatment of diseases due to their advantages such as being safer, having few or no side effects, and being natural. Many studies are conducted on medicinal plants and their phytochemicals regarding their health effects (Fierascu et al., 2021). Secondary metabolites found in plants are compounds that are effective in revealing biological effects. Secondary metabolites include many compounds such as essential oils, alkaloids, terpenes and phenolics. Separation processes and isolations are carried out to evaluate the effectiveness of these components (Teoh and Teoh, 2016). Essential oils isolated from plants have high biological activity. Much research has been done on the therapeutic and preventive effects of essential oils on several lung diseases (Horváth and Ács, 2015). The presence of functional chemical groups adds various properties to essential oils, such as antimicrobial, antibacterial, antioxidant and antifungal on lung (Li et al., 2023). Respiratory diseases are a worldwide health issue that contributes to global mortality. There are many diseases within the scope of respiratory tract, such as acute respiratory distress syndrome (ARDS), pulmonary fibrosis (PF), asthma, and chronic obstructive pulmonary disease (COPD). Drugs used in the treatment of such respiratory diseases have many side effects and are high cost (Cooke and Ernst, 2000). Using essential oils can be an effective way for respiratory problems (Leigh-de Rapper et al., 2021; Li et al., 2023).

1. ESSENTIAL OILS

Essential oils (EOs) are produced by the secondary metabolism of aromatic plants. A mixture of a class of organic compounds can be found in EO from many plants (Tisserand and Young, 2013; Sirousmehr et al., 2014). EOs are obtained by distillation from various organs of aromatic plants, such as flowers (rosemary, rose), leaves (seeds such as cumin, coriander, sage, mint, rosemary, thyme, basil, parsley, celery), fruits (lemon, fennel, anise), buds (garlic, cloves). The aromatic plants can produce EOs with organic compounds within the cytoplasm of plant cells through different routes, e.g. mevalonic acid or malonic acid (Prakash et al., 2015; Sharifi-Rad et al., 2017). The distinctive odor of EOs varies according to plant species and organs. Some EOs are dark in color, such as blue chamomile and green European valerian, while others are pale yellow and colorless. (Tisserand and Young, 2013). EOs include compounds that play a role in plant defense against pathogenic microorganisms and insects. They can also draw certain insects for pollination. Depending on the environment and geographic region, EOs have varying chemical compositions, which also impacts the percentage variables in them (Swamy et al., 2015; Arumugam et al., 2016).

1.1. Nature of EOs

Plant EOs are characterized by two main chemical groups: phenylpropanoids and terpenes. Although terpenoids and terpenes are the main constituents of EOs, in some plant species phenylpropanoids give this type of oil group a pleasant odor and taste. EOs are obtained by three chemical pathways: sesquiterpenes mevalonate, phenylpropenes shikimic acid and mono- and diterpenes methylerythritol (Başer et al., 2015). Secondary metabolites of a plant such as aldehydes, esters, terpenes, ketones, alcohols, ketones, and phenylpropanoids affect the chemical properties of EOs (Tohidi et al., 2019). Several isoprene groups condense to generate distinct terpene groups, including mono, di, tri, tetra, etc. (Sharma et al., 2017). Some enzymes that form terpenoids with chemical structures such as thymol, carvacrol, menthol, terpenes, aterpineol, geraniol and different positions in the hydroxic group modify the chemical structure. EO contains low amounts of compounds such as eugenol, cinnamaldehyde, and phenylpropanoid (Hyldgaard et al., 2012). The concentration and chemical content of EOs are different due to different characteristics of the plant such as harvesting period, drying, storage and distillation process (Fardhyanti et al., 2019).

The chemical properties of EOs vary according to the extraction methods used, sterochemical structure and species of the components. EOs are natural chemical combinations of 20-100 different volatile molecules that are responsible for defining EOs (Chouhan et al., 2017). In a study, the compounds of *Origanum* in EO were found to be 30% carvacrol and 27% thymol, while in Coriandrum this ratio was 68% linalool (Bakkali et al., 2008). The EO of *Mentha* is characterized by 19% menthone and 59% menthol content. The EO of *Anethum* leaves contained 31% limonene, 36% α-phellandrene and 58% carvone. limonene was also detected in the EO of *Anethum* seeds (Bakkali et al., 2008). Lavandula pubescens oil contains β-bisabolene (9.1%), carvacrol (13.4%) and carvacrol (55.7%); *Pulicaria incisa* contains 33% (El-Said et al., 2021).

1.2. Essential Oil Extraction

Plant EOs are analyzed using two methods: extraction of the oil (which takes many hours) and chemical analysis (which takes few minutes). The results of a previous study by Farhat et al. explain that several extraction procedures are used to refine plant EOs (Farhat et al., 2010). Hydro-distillation is a traditional system used to refine EOs in the laboratory due to their volatile nature. Steam distillation is also another traditional system used in industrial production to refine EOs (Sadeh et al., 2019). Extraction of EOs using various solvent solvents has been applied in industrial applications, but is restricted in food industries due to the toxicity of the organic solvents used (Pavlić et al., 2015). Different techniques for EO extraction such as microwave and ultrasonic assisted extraction and ohmic hydro-distillation system have been used in the industry to improve the sustainability, economy and efficiency of the applied system (Taban et al., 2018; Fardhyanti et al., 2019). Assuring the quality of essential oils is an important factor as improperly used extraction method can alter the chemical composition, quality and function of aromatic oils (Fardhyanti et al., 2019). Furthermore, if steam distillation is used in the EO extraction method, the chemicals obtained will always be volatile. Since the extraction methods used to obtain the composition of any oil are important, it is important to choose the appropriate extraction method for each plant.

Annual extraction of EOs should be carried out under the same conditions as using similar plant products maintains consistency in quality and quantity. The plants collected here must be dewatered, the flowers fresh and partially dried to be used in the extraction (Butnariu and Sarac, 2018).

1.3. Biological Activities of Essential Oils

Many herbs have been used by the food industry as flavouring, preservative and therapeutic sources since ancient times. In a large number of aroma plants, EOs are mainly responsible for the therapeutic effects. Many of the biological effects of EOs are not attributed to their key compounds, two or three of which are present in high percentages (Raut et al., 2014). To improve the sensory properties of medicinal products and for aromatherapy, essential oils are used in pharmacies. Different traditional systems use EOs to treat a wide range of health problems. For example, *Eucalyptus* EO is preferred to treat bronchitis and cough, sage and clove EOs to inhibit the growth of bacteria, Peppermint EO to treat respiratory congestion (Swamy and Sinniah, 2015; Swamy et al., 2016). Essential oils produced from various plants can be easily taken into the cell through the lung alveoli and skin epithelium. Terpenes and terpenoids are the main components of essential oils and are widely used in the treatment of many diseases. A large number of essential oils used industrially are reported to be a source of substitutes for many synthetic substances. It has also been reported that essential oils are not carcinogenic and can be safely used in foods to increase shelf life (Brenes et al., 2010). In the study conducted on lung and brain glioma cancer cell lines; the biological activities related to apoptosis of the extracts obtained from the flower and stem parts of the 'stone mint' plant known as *C. serpyllifolium subsp. serpyllifolium* were investigated. In the findings obtained, although *C. serpyllifolium subsp. serpyllifolium* has been used for many years in the treatment of diseases such as abdominal pain, stomach disorders, skin, diabetes, cough and healing of wounds in traditional methods, extensive literature research on the plant species has not been carried out in biological activity analyzes. Apoptosis and necrosis-mediated anticancer activities of *C. serpyllifolium subsp. serpyllifolium* plant have been investigated in more detail (Gezici et al., 2022). Borage oil obtained from *Borago officinalis* plant extracts in the Black Sea and Marmara Regions contains high levels of γ-linolenic acid (GLA) (Urrestarazu, Manuel Gallegos-Cedillo et al., 2018). GLA has been reported to have both anti-inflammatory and DNA protective effects. Fish oil and borage oils inhibit the biosynthesis of intrapulmonary proinflammatory eicosanoids to reduce pulmonary neutrophil accumulation, improving lung injury (Kast, 2001).

2. FIELDS OF ACTION OF AROMATHERAPEUTIC ESSENTIAL OILS

For EOs to be pharmacologically effective, they must enter the bloodstream through the nasal and pulmonary mucosa or diffuse directly into the limbic system of the brain. The level of aromatic compounds absorbed by these routes is lower than that of compounds taken by injection. Ingested EOs cross the blood brain barrier within 20 minutes and enter the active circulation (Herz, 2009). Signals transmitted by the olfactory nerves to the limbic system cause the brain to release hormones such as endorphins and serotonin and control the central nervous system (Mertas et al., 2015). EOs are currently used in the treatment of many diseases, either alone or in combination with certain drugs. In addition to their antidiabetic, antibacterial, antioxidant, antiviral, anti-inflammatory, antiprotozoal, sedative, antidiabetic, antibacterial, antioxidant, antiviral, anti-inflammatory, antiprotozoal, and sedative effects, EOs have been used in Alzheimer's and Parkinson's diseases, cardiovascular diseases, and even in regulating the circadian rhythm of the body (Boire et al., 2013).

3. EFFECTS OF ESSENTIAL OILS ON THE LUNG

Lung-related diseases are the leading cause of global deaths (Shaikh and Bhandary, 2021). The main reasons for the increase in respiratory diseases in recent years are occupational diseases that affect the lungs, air pollution and increased smoking levels. Respiratory diseases include asthma, chronic obstructive pulmonary disease, pulmonary fibrosis (COPD), and acute respiratory distress syndrome (ARDS) (PF). These are associated with pulmonary abnormalities, inflammation, and disturbances in lung function (Loo and Lee, 2022). Despite advancing medical technologies, no treatment option has yet been identified for inflammation in the lung. Treating lung inflammation involves relieving symptoms and lung damage with anti-inflammatory medications (Loo and Lee, 2022). Lung diseases such as COPD and asthma can be partially treated with bronchodilators and corticosteroids

(Timalsina et al., 2021). Due to the high cost of treatment of lung-related disorders and the increasing side effects of medications, there has been a need to seek other treatment strategies (Gautam et al., 2014). Essential oil used in respiratory treatment has become a subject of research for its therapeutic properties. When EOs are combined with conventional treatment, studies have shown that they relieve pain and reduce anxiety (Jaradat et al., 2016; Lakhan et al., 2016). EO can be administered through skin, oral and inhalation. Among all these different routes, inhalation is the most widely adopted method (Cooke and Ernst, 2000). EOs and the active ingredients in them play a role in lung disease pathophysiology as regulators. Numerous studies have reported that EOs show antioxidant, anti-inflammatory and antibacterial properties in respiratory diseases (Zielińska-Błajet et al., 2021).

4.TRADITIONAL USE OF EOS IN RESPIRATORY DISORDERS

Used for thousands of years, EOs are made from aromatic plants. Plant EOs date back to ancient Egypt and other civilizations. EOs were widely used in the Middle Ages for sterilization, plague prevention and health care (Cimino et al., 2021). Routes of administration of EOs include oral, inhalation, bath and massage (Xiao and Nakai, 2022). There is evidence that aromatic herbal medicines are used in the treatment of asthma, colds, respiratory diseases (Shingnaisui et al., 2018; Dalli et al., 2021). EOs therefore have medicinal value all over the world. Chinese Medicine, which dates back to before the 8th century, is today the most widely practiced traditional treatment system in every region of the world (Anonymous, 2001). When we look at the practices for COPD and asthma treatment in China, the majority of prescriptions consist of aromatic drugs. *Asarum heterotropoides*, *Zingiber officinale Rose*, *Schisandra sphenanthera Rehd*, *Triticum aestivum* account for 77% of aromatic Chinese medicines (Liu et al., 2021). The Greek physician Dioscorides states that a medicinal plant like *T. mongolicus* Ronn. is utilized to treat asthma (Jarić et al., 2015). To treat respiratory diseases people in Eastern Morocco have used traditional healing herbs such as *Mentha pulegium* L. (Jamila and Mostafa, 2014). Aromatic plants are commonly used in many nations because they are easy to use, have pharmaceutical efficacy, and have few adverse effects (Li et al., 2022).

4.1. EOs and Asthma

Asthma is distinguished by increased mucus secretion, chronic inflammation of the airways, and an increase in the number of inflammatory cells (El Gazzar et al., 2006). Cellular redox imbalance with Th1/Th2 balance transfer causes inflammation of airway in asthma (Balaha et al., 2012; Al-Khalaf, 2013; Jalali et al., 2013; Hardy et al., 2015). In addition, an important cause of asthma is the secretion of IL-17 by TH17 cells, which regulates neutrophil recruitment to the lung, disrupts the Treg/TH17 balance and reduces the anti-inflammatory effect of Treg cells (Luo et al., 2022). The balance between TH1/TH2 and Treg/TH17 is maintained by plant EOs and their components, who also restrict the growth of inflammatory cells, control pro-inflammatory proteins, and carry out anti-oxidation functions (Gandhi et al., 2020). It has been discovered that more than ten monomer forms of EO have strong inhibitory effects on inflammation based on neutrophils and eosinophils in asthma. Plants of various eucalyptus species have antibacterial, antioxidant, anti-inflammatory effects (Juergens et al., 2020). In a randomised study conducted to assess the use of *Soledum forte* as an adjuvant therapy in COPD, asthma and others, it has been shown that *S. forte* may have beneficial effects (Juergens et al., 2003; Worth et al., 2009). This medication can manage the progression of airway illnesses, improve airflow blockage, and minimize and improve shortness of breath (Juergens et al., 2003; Worth et al., 2009; Worth and Dethlefsen, 2012; Juergens et al., 2020). It is therefore an efficient medicinal compound in the control or prevention of inflammatory airway diseases. Studies with 1,8-cineole, which is present in many EOs, suggest that combination therapy enhances the therapeutic effect because of the anti-inflammatory properties of 1,8-cineole (Worth and Dethlefsen, 2012). Menthol is commonly found in *Mentha canadensis L mint* (Kamatou et al., 2013). In a clinical investigation, they discovered that when patients with asthma inhaled menthol vapor, their peak expiratory flow rate (PEFR) reduced dramatically (17.4 3.3% to 11.2 3.3%), and they concluded that menthol can reduce breathing (Tamaoki et al., 1995). *Origanum vulgare* L. and *T. mongolicus* Ronn are two plants that contain carvacrol. Carvacrol has been found in animal experiments that reduce airway inflammation in asthma by altering antioxidant, immunological, and anti-inflammatory properties. In an ovalbumin (OVA)-induced guinea pig asthma model, drinking water containing 80-160 g/mL carvacrol dramatically reduced serum IL-4 levels while increasing IFN- levels by modulating the TH1/TH2 balance (Jalali et al., 2013). In another investigation, carvacrol decreased serum NO, nitrites, and methacholine levels (Boskabady ve Jalali, 2013). It was discovered that the effects of 80 and 160 µg/mL carvacrol were much stronger than those of 50 µg/mL dexamethasone in both experiments. This confirms that carvacrol has the potential to be an effective treatment for autoimmunity, inflammation, allergies and other diseases. Carvacrol has been shown to have a significantly more potent relaxation effect than theophylline in an in vitro study of guinea pig tracheal chain (Boskabady and Jandaghi, 2003; Boskabady al., 2003). The mechanism of carvacrol may be related with the stimulatory effects of -adrenergic receptor antagonists, implying that carvacrol has abronchodilator potential (Boskabady et al., 2011).

4.2. EOs and COPD

COPD is a respiratory disorder that causes inflammation. Obstruction occurs in the airway due to inflammation (Decramer and Janssens, 2013). COPD is associated with emphysema and chronic bronchitis phenotypes (Sutherland et al., 2003). When the mechanism of COPD was examined, impaired cell repair, abnormalities in oxidative stress, and increased activation of inflammatory mediators were observed (Al-Azzawi et al., 2020). EOs contribute to treating COPD by inhibiting airway mucus secretion. Myrtol standardized (GeloMyrtol®/GeloMyrtol® forte) is an approved herbal medicinal product, distilled from a blend of EOs such as *Rhodomyrtus tomentosa*, eucalyptus, *Citrus limon* and oils *Citrus sinensis*, which act as mucus and secretion solvents (Beeh al., 2016; Fürst et al., 2019). Additionally, standardized oral intake of myrtol has been reported to improve phlegm and cough symptoms and reduce acute worsening of COPD. In addition, Myrtol is commonly administered as an adjuvant treatment for COPD (Rantzsch et al., 2009; Juergens et al., 2018). Myrtol has been standardized. Cineole is available in standardized form. Myrtol, used in the treatment of COPD, is a component that suppresses mucus secretion and also has antioxidant and anti-inflammatory properties (Prall et al., 2020). According to a study, the effects of 1,8-cineole were investigated on the lung. It has been determined that lung functions are restored due to the treatment applied three times a day (Worth et al., 2009). According to these results, an improvement was observed in the patients' degree of shortness of breath. This mainly showed that in the treatment of COPD, 1,8-cineole modulates symptoms and is associated with exacerbations. Respiratory tract infections are more susceptible in patients with COPD when mucociliary clearance is impaired (Tilley et al., 2015). Oral cineole treatment at a dose of 260 mg/kg decreased the lung colonization number of *Haemophilus influenzae* by 1.3-fold in a rat experimental animal model of cigarette smoke (CS)-induced COPD. Cineole inhibited MUC5AC expression to suppress the level of ciliary mucus and protected the lungs from bacterial infection in rats (Yu et al., 2019). Moreover, the amelioration of CS-induced inflammation in mice by cineole has been demonstrated by reducing the levels of many inflammatory agents, including TGF-β1, TNF-α, TGF-β1, IL-1β, IL-6, and NF-κB. According to the data obtained, it was concluded that cineole is an effective compound for the treatment of COPD. Another study examined carvacrol in an animal model of CS administration. Carvacrol has been found to inhibit inflammation and prevent oxidative damage in the lung. Carvacrol administered at concentrations of 120 and 240 μg/mL was compared to administration of 50 μg/mL dexamethasone, and it was reported that the effect of carvacrol was parallel to that of dexamethasone and was more effective (Boskabady et al., 2015; Mahtaj et al., 2015). According to a study conducted on carvacrol, it was found that it has a healing effect on emphysema. It has been noted that carvacrol exerts its effect by suppressing NF-κB signaling (Games et al., 2016).

In summary, EOs work primarily by lowering inflammation in COPD and other inflammatory lung disorders such as asthma, delaying disease progression through oxidative stress. By enhancing the activities of different antioxidant enzymes, the use of EOs like eucalyptus oil as adjuvant therapy to address oxidative stress also reduces disease pathology and delays the progression of the disease (Pourgholamhossein et al., 2016). Many traditionally used medications have difficulty improving lung inflammation. Because these drugs cannot suppress inflammation by acting differently on the enzymes involved in antioxidant mechanisms (Dozor, 2010). Known drugs used in COPD, such as mitogen-activated protein kinase p38 (MAPK p38) inhibitors and NF-κB inhibitors, do not suppress inflammation (Dua et al., 2019). Symptoms of bacterial and influenza infections that occur additionally in COPD can be improved with EO. Because EO has many biological activities including antibacterial, anti-inflammatory and antiviral. In clinical studies, it has been noted that compounds such as Myrtol and cineole, which have essential oil properties, can improve lung inflammation and reduce the symptoms of the disease (Worth et al., 2009; Worth and Dethlefsen, 2012).

4.3. EOs and pneumonia

A fungal, viral, or bacterial infection of the lower respiratory tract that affects the lungs and surrounding tissues is known as pneumonia (Horváth et al., 2015). However, bacteria like *Staphylococcus aureus* and *Pseudomonas aeruginosa* form biofilms to withstand antibacterial therapy to defend themselves from substances like immune cells and antimicrobials (Tacconelli et al., 2018). Based on their hydrophilic or hydrophobic properties, chemical content and microorganism type, EOs act as inhibitors of the growth of microorganisms (Reyes-Jurado et al., 2020). The membrane of bacterial cells and the cell wall are antibacterial targets for essential oils. Essential oils have contributed to the production of ATP and pH homeostasis, as well as affecting cell transcriptomes and proteome systems (Horváth et al., 2015). Inhibiting the synthesis of bacterial biofilms, and in preventing the removal of maturing bacteria, some EOs have antibacterial properties (Kowalczyk et al., 2020). Antiviral activity from EOs via inhibition of virus host receptors, viral growth, viral protein synthesis and inflammation properties suggests anti-influenza role. Traditionally the *Mosla dianthera Thunb* has been used, for example. It is used in the treatment of headaches, fevers, coughs, colds and bronchitis. Oral administration of 90-360 mg/kg of *Mosla dianthera* Thunb EO to mice infected with influenza virus A resulted in considerable pneumonia suppression. The mechanism may be linked to reduced production of cytokines (IFN-γ and IL) (Wu et al., 2012). It was discovered that eucalyptus EO (Sharma and Kaur, 2020) and *Allium sativum* L. EO (Thuy et al., 2020) have anti-severe acute respiratory syndrome (SARS) coronavirus effects through numerous targets during the global COVID-19 pandemic. In a prior clinical research, after receiving effective mucolytic therapy, a 3-year-old girl with respiratory syncytial virus pneumonia complicating restrictive lung disease was still requiring oxygen inhalation. Following the administration of an essential oil blend comprising of *Sophora flavescens* Ait., *L. angustifolia* Mill., *Thymus vulgaris*, and *M. canadensis* by passive inhalation, the child's symptoms showed improvement and their oxygen consumption declined considerably (Hedayat, 2008). Despite the fact that EOs have been shown to exhibit antiviral and antibacterial properties in vitro, there is currently little experimental support to cure pneumonia brought on by bacteria or viruses in vivo. Consequently, EOs' antiviral properties provide pharmaceuticals intended to treat viral infections and multidrug resistance with a new therapeutic approach. For this reason, a large amount of clinical evidence needs to be obtained through in vitro studies. Data from these studies show that EOs have the potential for use as adjuvant medicinal products in respiratory tract infections. Moreover, it is possible that EOs could be toxic to humans and so their concentrations have to be correctly measured. Cicloral is a highly antibacterial and does not qualify as a potential medicinal product, due to the fact that some of these studies showed higher levels of cytotoxicity (Kumari et al. 2017).

5. CONCLUSION

Essential oils have many biological characteristics that make them an effective natural alternative for controlling a wide range of diseases, which makes them valuable for maintaining human health. To increase patient survival rates and quality of life, interventional treatments and primary preventative therapies must be implemented. In public opinion, EOs are often considered as complementary and adjunctive medical treatments. For pulmonary disorders, EOs require ongoing investigation to identify their potential application in an era where personalized medical treatment is available. Personalized precision treatment options and preventive approaches can be achieved with EOs because they may have more potent effects than a single medicine.

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CHAPTER 9

COMPARISON OF NUTRIENT ELEMENT CONCENTRATIONS OF SOME SPECIES BELONGING TO THE LAMIACEAE FAMILY

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DOI: https://dx.doi.org/10.5281/zenodo.10454603

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INTRODUCTION

There are approximately 236 genus and 7173 taxa belonging to the Lamiaceae family in the world. In Turkey, this family is represented by 46 genus and 755 taxa. Plants in this family are medicinal and aromatic plants of economic importance due to the secondary metabolites they contain. Thanks to these secondary metabolites, it is widely consumed as tea and spice (Balos, 2022). *Thymus pectinatus, Sideritis libanotica, Salvia cryptantha* species belong to the Lamiaceae family. (Demirtaş et al. 2011; İpek et al. 2012; Manshad et al. 2014). *Thymus pectinatus* is generally referred to as “thyme”, *Salvia cryptantha* is called “sage” and *Sideritis libanotica* is known as “mountain tea”. The chemical components of *Thymus pectinatus* are thymol, p-cymene and γ-terpinene (Başer et al. 1999), the chemical components of *Salvia cryptantha* are 1.8-cineole, camphor, α-pinene, camphene (Doğan et al. 2017), the chemical components of *Sideritis libanotica* are hexadecanoic acid (Formisano et al. 2015). Thymus species are used in alternative medicine in the treatment of diseases such as rheumatism, arthritis and bronchitis (Saygın et al. 2018; Ergül et al., 2021). It is also used as a cramp reliever, disinfectant, reliever of upper respiratory tract infections, appetite stimulant, stimulant of the digestive system, and against nervous system weakness and intestinal diseases (Anonymous, 2005). Salvia species are effective in combating infections and exhibit antimicrobial as well as anti-cancer properties (Kamatou et al. 2008). Sideritis species are widely used for colds and stomach aches (Schmeda-Hirschmann and Yesilada, 2005).

Various factors such as the type of plant, its age, root growth, physical, chemical and biological properties of the soil, and the types and amounts of nutrients available to the soil affect the amounts of nutrients found in plants (Kacar and Katkat, 2007). Plants growing in soil rich in beneficial nutrients absorb relatively more nutrients. In this study, it was aimed to determine the nutrient element concentrations of some species belonging to the Lamiaceae family growing naturally in Sivas province.

1. MATERIAL AND METHOD

1.1. Macro and Micro Nutrient Element Analysis

Sideritis libanotica, *Thymus pectinatus*, *Salvia cryptantha* plants collected from nature were washed with pure water, 0.1 N HCl and pure water again in the laboratory for macro and micro element determinations, and then dried at 65 °C for 48 hours. Dry plant samples were ground into powder in an agate mill and then weighed as 0.2 g and wet digested in a microwave device (Milestone Ethos Easy Advanced Microwave Digestion System, Italy) with an H_2O_2-HNO_3 acid mixture (2 mL 35% H_2O_2, 5 mL 65% HNO_3) has been made. According to Murphy and Riley, (1962), phosphorus concentration is measured colorimetrically in a spectrophotometer at 882 nm; calcium, magnesium, potassium, iron, manganese, zinc and copper concentrations were determined on the Atomic Absorption Spectrophotometer device (Shimadzu AA-7000, Japanese).Nitrogen concentrations were determined according to the Kjeldahl distillation method (Bremner, 1965). In the study, each analysis was performed three times.

2. RESULTS

N, P and K concentrations of some species belonging to the Lamiaceae family (*Sideritis libanotica*, *Thymus pectinatus*, *Salvia cryptantha*) collected from different regions of Sivas province are given in Table 1, Ca and Mg concentrations are given in Table 2, Fe, Zn, Mn and Cu concentrations are given in Table 3.

Table 1. N, P and K concentrations of some species belonging to the Lamiaceae family

Plant Species	**N**	**P** (%)	**K**
Sideritis libanotica	1.41±0.21	0.043±0.01	1.06±0.09
Thymus pectinatus	1.35±0.15	0.057±0.00	1.37±0.11
Salvia cryptantha	1.15±0.14	0.085±0.00	2.36±0.10

When Table 1 was examined, it was determined that the highest nitrogen concentration was in the *Sideritis libanotica* species with 1.41%, followed by *Thymus pectinatus* and *Salvia cryptantha* species with 1.35% N and 1.15% N, respectively. When phosphorus concentrations were evaluated, unlike nitrogen concentrations, the highest was detected in *Salvia cryptantha* species with 0.085% P. While 0.057% P was determined in the *Thymus pectinatus* species, the lowest phosphorus concentration was determined in the *Sideritis libanotica* species with 0.043% P. Potassium concentrations of different species belonging to the Lamiaceae family were found to be similar to the phosphorus results. The highest potassium concentration was determined in the *Salvia cryptantha* species with 2.36% K, while the lowest was determined in the *Sideritis libanotica* species with 1.06% K. Bayram (2018) found in plant samples taken from ten producers growing organic Izmir Thyme

(*Origanum onites* L.), a different genus belonging to the Lamiaceae family from Denizli province, that their nitrogen concentration was 0.69 % N on average, their phosphorus content was 0.28% P on average, and potassium contents were reported to be 2.67 % K on average. A different species (*Salvia fruticosa* Mill.) with different organic fertilizers in sage plant, the highest N, P and K concentrations were determined as 2.42% N, 0.40% P and 2.67% K, respectively (Kocabaş et al., 2007). In a study, plant growth regulators were applied to another thyme species (*Origanum onites* L.) and the average nitrogen, potassium and phosphorus were found to be 1.13% N, 3.29% K and 2427.5 ppm P, respectively (Baydar and Erdal, 2004).

Table 2. Ca and Mg concentrations of some species belonging to the Lamiaceae family

Plant Species	**Ca**	**Mg**
	(%)	
Sideritis libanotica	1.35±0.12	0.48±0.05
Thymus pectinatus	2.31±0.18	0.53±0.04
Salvia cryptantha	3.41±0.17	1.25±0.07

Calcium and magnesium concentrations of different species belonging to the Lamiaceae family were also found to be similar to phosphorus and potassium concentrations (Table 2). The highest calcium and magnesium concentrations were found in the *Salvia cryptantha* species (3.41% Ca and 1.25% Mg, respectively). This species is followed by *Thymus pectinatus* species with 2.31% Ca and 0.53% Mg, while the lowest calcium and magnesium concentrations were determined in *Sideritis libanotica* species with 1.35% Ca and 0.48% Mg. In their study with a different species of sage plant (*Salvia fructicosa* Mill.), Kocabaş et al

(2007) applied different organic fertilizers and found the highest Ca and Mg concentrations to be 2.33% Ca and 0.42% Mg, respectively. Bayram (2018) reported that in a study on İzmir thyme plant, it was found the calcium content to be 2.45% Ca on average and the magnesium content to be 0.31% Mg on average.

Table 3. Fe, Zn, Mn and Cu concentrations of some species belonging to the Lamiaceae family

Plant Species	Fe	Zn (mg kg^{-1})	Mn	Cu
Sideritis libanotica	165.2±14.5	23.1±2.11	22.5±2.45	8.9±0.90
Thymus pectinatus	845.9±21.4	26.5±1.47	67.9±4.44	9.9±0.89
Salvia cryptantha	215.9±17.4	27.8±1.24	200.4±7.87	17.1±1.99

When Table 3 was examined in terms of microelements, it was determined that the highest iron concentration was in the *Thymus pectinatus* species with 845.9 mg Fe kg^{-}1. The lowest iron concentration was found in the *Sideritis libanotica* species with 165.2 mg Fe kg^{-1}, while it was determined to be 215.9 mg Fe kg^{-1} in the *Salvia cryptantha* species. Among the microelements, the highest concentrations of zinc, manganese and copper were detected in the *Salvia cryptantha* species as 27.8 mg Zn kg^{-1}, 200.4 mg Mn kg^{-1} and 17.1 mg Cu kg^{-1}, respectively. The lowest concentrations were found in the *Sideritis libanotica* species as 23.1 mg Zn kg-1, 22.5 mg Mn kg^{-1} and 8.9 mg Cu kg^{-1}, respectively. In a study conducted with different types of thyme, the average iron, zinc, manganese and copper concentrations were determined as 179 mg Fe kg^{-1}, 28 mg Zn kg^{-1}, 71 mg Mn kg^{-1} and 24 mg Cu kg^{-1}, respectively (Bayram, 2018). Baydar and Erdal (2004) reported that they found an average of 78.10 mg Fe kg^{-1}, 63.15 mg Zn kg^{-1} , 57.80 mg Mn kg^{-1} and

4.90 mg Cu kg^{-1} in the İzmir thyme (*Origanum onites* L.) plant to which they applied a plant regulator in Isparta province. Also, they reported that thyme is a spice rich in macronutrients, especially K and Ca, and micronutrients such as Na, Fe, Zn and Mn.

In the research, nutrient element concentrations of some species belonging to the Lamiaceae family growing naturally in Sivas province were determined. When the findings were evaluated as a whole, it was determined that the species with the highest nutrient element concentrations was *Salvia cryptantha*, and the species with the lowest nutrient element concentrations was *Sideritis libanotica*.

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CHEAPTER 10

AROMATHERAPY APPLICATIONS IN WOMEN'S HEALTH

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DOI: https://dx.doi.org/10.5281/zenodo.10454607

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INTRODUCTION

Aromatherapy is a word derived from the Greek word aroma, which means scent and therapy (Öz, 2020). The use of aromatherapy applications, which have been frequently preferred in the treatment of diseases since the history of Ancient Egypt and the Middle East, dates back approximately 5,000 years (Terzi et al., 2020; Bilgiç, 2017). Aromatherapy, which is one of the alternative and complementary medicine methods and stands out as a branch of phytotherapy, is a practice in which the therapeutic properties of the oils obtained from plants through various processes are used (Aćimović, 2021). According to another definition, aromatherapy is a method in which intensely concentrated oil extracts obtained from plants by distillation and squeezing, and scents are used to ensure both physical and spiritual well-being of individuals (Shaterian et al, 2021; Ali et al., 2015).

Aromatherapy, used as a holistic therapy, activates mental activities, slows down or interrupts the transmission of pain signals, stimulates the release of endorphin hormone, and can be applied with manual techniques. When the psycho-emotional effects of essential oils are combined with the application techniques of aromatherapy, body and mind relief can be achieved (Bertone and Dekker, 2021). Aromatherapy can be applied orally, topically (via touching, compressing or bathing), internally (gargle, vaginally, anal suppository) and inhalation (indirectly or directly via steam or non-steam breathing). These oils affect the central nervous system with the neurohormonal message sent to the limbic system and create a state of sedation and relaxation in the person (Heydarirad et al., 2019; Bilgiç, 2017).

The World Health Organization (WHO) emphasizes that complementary medicine treatments play a significant role in the treatment of chronic diseases or in the improvement of the quality of life. As of 2014, the WHO also recommended that courses should be organized in this field and that aromatherapy applications should be performed to reduce anxiety and stress and to alleviate or eliminate pain (WHO, 2013). Since aromatherapists discovered the skin permeability and antiseptic properties of the essential oils used for aromatherapy, their usage areas have become increasingly widespread (Sharma et al., 2021). The use of aromatherapy for therapeutic purposes, which is traditionally applied in many countries such as China, Greece, Switzerland, Iraq, Syria, India, England and the United States, is quite common (Buckle, 2015).

1. AREAS IN WHICH AROMATHERAPY IS USED IN WOMEN'S HEALTH PRACTICES

Aromatherapy, widely used in many areas, is also preferred to improve women's health and welfare. Among women's health problems for which aromatherapy is used are premenstrual syndrome (PMS), symptoms that occur during pregnancy, labor pain, infertility, vaginal infections and menopausal symptoms (Lakhan et al., 2016). In addition, aromatherapy is also used as an effective method in situations such as stress management, mood control, state of arousal, improvement of memory, immunological problems and management of symptoms of dementia (Bilgiç, 2017 ; Özdemir and Öztunç, 2013).

The plants most commonly used in aromatherapy in the field of women's health are rose, mint, lemon, ylang-ylang, geranium, lavender, orange jasmine, sage, clove, and *Boswellia carterii* (Frankincense) essential oil (Akgün and Çakır, 2022).

2. AROMATHERAPY APPLICATIONS IN THE MANAGEMENT PREMENSTRUAL SYNDROME (PMS)

During the luteal phase of the menstrual cycle, women may experience some physical, psychological and behavioral symptoms. These symptoms disappear within about one to four days from the start of the menstrual period. The main ones of these symptoms, called premenstrual syndrome (PMS), are mood changes, anxiety, depression, sleep disorders, bloating, tenderness in the breasts and lethargy (Matsumo et al., 2013).

The mechanism of action of aromatherapy on PMS is explained by the effect of aromatherapy essential oils on the limbic system. These essential oils enter the body through breathing. These molecules entering the body send electrochemical stimulation to the olfactory regions in the hippocampus, hypothalamus and limbic system in the brain. These systems help alleviate symptoms by influencing the shaping of emotions and management of thought processes (Es-Haghee et al., 2).

In several studies, it has been demonstrated that aromatherapy practices play a significant role in reducing PMS symptoms. In their study conducted with university students experiencing PMS, (2018), Uzunçakmak et al. concluded that the students' symptoms such as pain, anxiety, depressive mood, bloating, depressive thoughts and irritability decreased as they used lavender oil by inhalation method.

In another study conducted with women of reproductive age in which lavender oil was used, it was determined that inhalation of lavender oil was effective in improving parasympathetic nervous system activity and reducing premenstrual emotional symptoms (Matsumo et al., 2013).

In their study conducted with students experiencing PMS syndromes (2018), Lotfipur-Rafsanjani et al. investigated the effects of geranium essential oil and sweet almond oil on the students' PMS syndromes, and concluded that massage performed with these oils was effective in reducing the physical and psychological effects of PMSs. In their study (2018), Heydari et al. determined that the application with *Citrus aurantium* flower had a positive effect on the improvement of (improved) PMS.

3. USE OF AROMATHERAPY DURING PREGNANCY

Since pregnancy is a period in which women experience several physical and psychological changes, they need an effective method to cope with these changes. During this period, pregnant women experience various complaints such as nausea, vomiting, fatigue, urinary system infections, pain, stria gravidarum, constipation, edema, etc., which can negatively affect the quality of life of pregnant women. Alleviation of these complaints experienced by pregnant women is considered necessary in order to improve their well-being, and to ensure that the pregnancy process continues healthily (Sülü Dursun et al., 2022). The use of aromatherapy is among the preferred methods in the management of symptoms caused by physical and psychological changes that occur in pregnant women during this period (Sülü Dursun et al., 2022).

It has been reported that using the oils from the following plants during pregnancy is considered safe: mint, lemon, chamomile, rose, tea tree, orange flower, jasmine, ylang ylang, cardamom, bergamot, bitter orange, geranium, tangerine, sandalwood, lavender, lemon balm (melissa), eucalyptus and patchouli (Teskereci and İlkay, 2020). Essential oils and symptoms they relieve during pregnancy are as follows: peppermint oil (*Mentha piperata*): nausea and vomiting, anxiety, indigestion, muscle ache and headache; Lavender oil (*Lavandula* sp.): anxiety, fatigue, stress; Rose oil (*Rose damanscena* or centifolia): pain, constipation, anxiety, fear; Tea tree oil (*Melaleuca alterniflolia*): urinary tract infection, vaginal infections, colds; Bergamot oil (*Citrus aurantium*/Bergamia): nausea, stress; Grapefruit oil (Citrus x Paradisi): depression, anxiety, nausea, cold, headache; Jasmine oil (*Jasminum officinale*): anxiety and stress; Ylang Ylang oil (*Cananga odorata*): mild preeclampsia, fear, anxiety; Roman chamomile oil (*Chamaemelum nobile*/*Anthemis nobilis*): indigestion, leg cramps, insomnia, constipation; Sweet orange oil (*Citrus sinensis*): edema, insomnia, skin irritations and fatigue (Tiran, 2018; Tiran, 2021).

Using bitter almond oil, cocoa oil, rosehip oil and olive oil is effective in the treatment of stria gravidarum occuring during pregnancy (Teskereci and İlkay, 2020; Şen et al., 2020). In their study conducted with pregnant women, Effati-Daryani et al. concluded that lavender oil application significantly reduced the level of fatigue in pregnant women (Effati-Daryani et al., 2018). In their study conducted with pregnant women in 2017, Shirazi et al. determined that rose oil reduced back pain experienced during pregnancy (Shirazi et al., 2017).

4. USE OF AROMATHERAPY DURING LABOR

Although birth is considered as a natural process, women experience changes that will affect or challenge them psychologically in addition to physiological changes. In this process, health professionals utilize aromatherapy applications to reduce women's stress, to relax them and to ensure a healthy progress of the birth process (Ergin and Mallı, 2019). In a study conducted to determine pregnant women's preferences for the applications through which aromatherapy was performed during labor, of the women, 37% preferred absorbent paper with drops of essential oil, 32% preferred massage, 20% preferred birthing pool, 4% preferred aromatherapy compress, and 54% preferred foot bath (Burns et al., 2007).

Aromatherapy applications used during labor and their effects are as follows: Sage; to reduce pain and increase contractions; Eucalyptus: to reduce nasal congestion; Lavender: to relieve pain and anxiety; Ylang-ylang: to reduce depression and promote relaxation; Lemon: to reduce symptoms of pain, anxiety and depression; Mint oil: to relieve nausea and vomiting; Rose: to reduce anxiety and provide comfort; Orange oil and Tangerine: to achieve relaxation; Jasmine: to reduce pain and depression; Roman chamomile: to reduce back pain and provide relaxation (Michal et al., 2018; Ergin and Mallı, 2019; Lamadah and Nomani, 2016).

In their study conducted with nulliparous women (2018), Esmaelzadeh-Saeieh et al. used *Boswellia carterii* (Frankincense) essential oil and concluded that it significantly reduced the severity of labor pain. In their review of 17 studies (2018), Chen et al. concluded that aromatherapy applications shortened the duration of the third stage of labor, reduced labor pain in the transition phase, but had no effect on parameters such as premature rupture of membranes, emergency cesarean section or spontaneous onset of labor (Chen et al., 2018).

In their eight-year study in which 8058 mothers were included (2000), Burns et al. concluded that the most effective aromatherapy agent used in aromatherapy was lavender oil. They also concluded that aromatherapies reduced the mothers' anxiety, fear and pain levels (Burns et al., 2000). In general, aromatherapy applications used during labor relieve birth pain, reduce anxiety and stress in women, shorten the duration of birth and increase maternal satisfaction (Vakilian et al., 2018; Lamadah and Nomani, 2018; Michal et al., 2018; Esmaelzadeh-Saeieh et al., 2018; Yazdkhasti and Pirak, 2016).

5. USE OF AROMATHERAPY DURING THE POSTPARTUM PERIOD

The postpartum period which starts with the birth of the fetus and covers a period of approximately 6-8 weeks is a sensitive period during which the mother experiences psychological and physiological changes. During this period, preventing any complications likely to occur in the mother, improving her welfare level, and diagnosing and treating the emerging problems early are of great importance (Aarestrup et al., 2020).

Essential oils obtained from plants such as rose, rosemary, lavender, cinnamon, jasmine, ylang-ylang plant, sandalwood and patchouli are used in aromatherapies for the treatment of postpartum anxiety and depression. These oils ensure the secretion of endorphin hormones in the individual's body and relaxation of his or her muscles, nourish cells and tissues, and increase oxygenation. Thanks to all these effects, essential oils used in aromatherapy help improve sleep quality by reducing pain, anxiety, spasm, and fatigue (reduce pain, anxiety, spasm, and fatigue, and thus help improve sleep quality) (Rezaie-Keikhaie et al., 2019).

In their systematic review of 15 studies, Tsai et al. reported that aromatherapy applied in the postpartum period had a positive effect on (positively affected) women's depression, fatigue, anxiety, nipple crack pain, episiotomy pain, post-cesarean pain, nausea, and sleep problems, and that these practices did not have any serious side effects on women

(Tsai et al., 2020). In their study, Tosun and Pınar applied dry cupping together with lavender oil to assess their effect on perineal pain occurring in the postpartum period and concluded that this application reduced perineal pain (Tosun and Pınar, 2021). In their study, Chen et al. concluded that bergamot oil therapy did not improve sleep quality of the women who were in the postpartum period, but alleviated their depressive mood (Chen et al., 2022).

In their study, Çobanoğlu and Şendir investigated the healing effect of St. John's wort (*Hypericum perforatum*) oil on episiotomy in the women in the postpartum period, and determined that St. John's wort oil reduced pain, ecchymosis, redness and edema in the women having undergone episiotomy (them) (Çobanoğlu and Şendir, 2020). Our general review of the literature demonstrated that aromatherapy appeared to be effective in reducing episiotomy pain, relieving anxiety and improving mood in women in the postpartum period (Yılmaz et al., 2023).

6. USE OF AROMATHERAPY DURING MENOPAUSE

Menopause is the complete cessation of menstruation associated with hormonal changes and occurs naturally in most women (Johnson at al., 2019). During menopause, women experience several physiological and psychological changes such as hot flashes, headache, night sweats, dizziness, nausea, anxiety, loss of appetite, sleep problems, depression, memory problems, sexual problems, and urogenital problems (Delamater and Santoro, 2018; Santoro et al., 2015). Essential oils used in aromatherapy during menopause have been determined to alleviate the symptoms women experience during this period (Kilci and Ertem, 2019).

In a meta-analysis conducted with women in the postmenopausal period, the authors concluded that aromatherapy application significantly improved the women's psychological symptoms (Babakhanian et al., 2018). In their study conducted with women in the menopausal period (2019), Roozbeh et al. determined that lavender oil had a positive effect on the women's physical, psychological and vasomotor symptoms, improved their sleep quality in this period and had positive effects on sexual desire. Lotfipur-Rafsanjani et al. (2015) conducted a study using geranium oil and almond oil for half an hour once a week for eight weeks, and determined that the depression rate was lower in women in the experimental group who received aromatherapy than it was in the women who did not.

7. ISSUES TO BE CONSIDERED WHEN AROMATHERAPY IS IMPLEMENTED

Although in several studies the benefits of aromatherapy have been proved, it should be kept in mind that there may be negative consequences when these oils are used. Thus to ensure the effectiveness of aromatherapy and to prevent negative consequences, the following issues should be taken into consideration (Bilgiç, 2017; Buckle, 2003; Özdemir and Öztunç, 2013):

- Essential oils should be stored in suitable conditions, in dark glass bottles and in places out of direct sunlight.

- It should be taken into account that complications such as skin irritation and burns when oils are applied through the skin might develop, that the effects and side effects of the applied oils should be known and that precautions should be taken accordingly.

- Usage areas, qualities and application methods of essential oils should be known.

- Essential oils should be diluted before their application.

- It should be kept in mind that increasing the application dose of the oils to increase their effect is harmful and that they should be applied in appropriate doses.

- It should be considered that aromatherapy applied through inhalation poses the risk of developing toxic reactions. Thus, it should be performed in environments where ventilation conditions are appropriate.

- Contact of essential oils with mucous membranes and eyes should be avoided.

- It should not be forgotten that the types of essential oils preferred especially during the first, second and third trimesters of pregnancy are different and limited in number.

- It should be questioned that from which plant the oil to be used in aromatherapy is produced. For instance, while "*Lavandula stoechas*", a type of lavender, causes abortion during pregnancy, the use of another type, "*Lavandula angustifolia*", is useful during pregnancy.

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CHAPTER 11

THE EVALUATION OF HENNA PLANT (*Lawsonia inermis*) AS AN ORGANIC DYE SUBSTANCE IN WOOL FIBERS FOR SUSTAINABLE TEXTILES

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DOI: https://dx.doi.org/10.5281/zenodo.10454611

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INTRODUCTION

With the continuous increase in demand for eco-textiles, natural dyes have gained attention as an alternative to synthetic dyes. Some natural dyes are abundantly available, easily accessible, less harmful to human health and the environment, and possess a wide range of functional applications (Adeel et al., 2018; Haddar et al., 2018; Zhou et al., 2020). Natural dyes, containing various chemical components such as anthraquinones, alkaloids, indigoids, anthocyanins, flavonoids, tannins, and carotenoids, are produced by different plants, animals, and microorganisms and can be applied in coloring textile materials (Amin et al., 2020; Barani et al., 2018; Fazal-ur-Rehman et al., 2020; Haji et al., 2022).

Since plants are derived from nature and are abundantly available, they have become the most preferred type among natural dye groups. In earlier times, certain plants were chosen to dye textile products such as fibers, yarns, and fabrics. Some plants were also used to color parts of the human body (hands, feet, skin, face, hair, nails) for aesthetic purposes. At times, they were employed in traditional folk medicine as natural remedies. The plant involved in this study, henna (*Lawsonia inermis*), has captivated human interest throughout history and has been used in various places for dyeing and medicinal purposes. However, despite its ability to produce beautiful colors, henna has not been extensively utilized as a dye in the textile field. With the increasing environmental consciousness in the global community within the ecological system, environmentally friendly products are being preferred for sustaining future life quality.

In a world where concepts such as a green environment and green textiles are rapidly gaining prevalence, it has been understood that the wastewater resulting from the chemical dyeing process causes harm when mixed with nature. While chemical dyes cannot be entirely abandoned, there is a quest for methods and raw materials that inflict lesser harm on the world, nature, and human life. With the growing environmental awareness, researchers have accelerated interdisciplinary studies and explored alternative new methods to chemical dyes. Alongside natural dyes, initiatives have been launched to expand the production and usage of natural fibers. Cost reduction measures have been employed in fiber production by utilizing waste parts of plants (such as artichoke stems, banana peels). Ongoing research is being conducted on numerous plants to contribute to natural dyeing studies. To enable colors obtained from plants to be used on natural fibers like wool, cotton, silk, their effects on fibers and the colorfastness values should be measured (Kaynar & Tonus, 2022).

The aim of the research is to contribute to the evaluation of henna (*L.inermis*), a plant proven to have health benefits used in the treatment of many diseases, as a dye substance within the scope of sustainable green textiles. Ongoing research on numerous plants aims to contribute to natural dyeing studies. In order to assess the viability of natural dye extracts obtained from plants for use on natural fibers such as wool, cotton, silk, and linen, their effects on fibers (light, rubbing, and water droplet fastness) need to be measured to determine their durability values.

1. HENNA PLANT *(Lawsonia inermis)*

Henna (*L. inermis*), which has been used in the treatment of many diseases throughout history, belongs to the Lythraceae family and is a flowering plant that grows 2-6 meters in height. While its native land is Northeast Africa, it is cultivated in various countries today, including all of North Africa, India, Pakistan, and Sri Lanka. The historical journey of henna dates back to ancient times. The earliest known use of henna in history is its application on the nails and bandages of mummies in Ancient Egypt. Furthermore, it is reported that henna has been a common embellishment tool, particularly among women, for extended periods, and it is frequently used in rituals in North Africa and the Middle East (Karaca & Şar, 2008).

The historical development of henna dates back to ancient times. Its use in Ancient Egypt, not only as a dye but also in medicine as a remedy, as well as the application of henna on the nails of mummies, demonstrates that henna has been utilized for various purposes since ancient times (Yardımcı, 2008).

Determining the history and origins of henna, and where interactions and traditions began over centuries of migrations and cultures, is challenging. The earliest presumed uses of henna are believed to have occurred between 7500 and 3500 BC, likely during the final Ice Age in Africa when the Sahara region was thought to be greener than it is today. Evidence suggests that the Neolithic people living in Çatalhöyük around 7000 BC adorned their hands with henna to establish connections with fertility goddesses. Red-marked hands associated with fertility rituals and a red bull deity found at Çatalhöyük are cited as evidence indicating the use of henna as a red coloring dye (Cartwright-Jones, 2006; Dalan-Polat, 2020).

Henna is still used for various purposes in folk remedies today. It is said that a mixture created by boiling henna with chamomile flowers, adding a teaspoon of alum, a teaspoon of black pepper, applying it to the head, leaving it for a day, and then washing it off, is beneficial against colds. It is known that for bronchitis, henna seeds mixed and pounded with seedless black grapes and consumed as a pill in the morning and evening can be beneficial. Additionally, henna is used in folk practices as a strengthener for the eyes and to alleviate fatigue. It is widely known that elderly women often burn henna on their heads for strengthening the eyes. There is a prevalent belief that henna is the most effective folk remedy for treating eczema, fungal infections, burns, cuts, and cracks on fingertips after laundry (Yardımcı, 2008).

1.1. Henna Plant In Turkısh Folk Medıcıne (*Lawsonia inermis*)

The word 'henna,' derived from the Arabic term 'hinna,' has been integrated into our language and holds significant importance in Turkish folk culture for traditional ceremonies, medicinal purposes, and cosmetics (Dursunoğlu, 2014).

According to Dalan Polat (2020), information about the use of henna in medicine and cosmetics is found in the Ebers Papyrus, which dates back to around 1500 BC (Bryan & Smith, 1974). "In 1875, German Egyptologist Georg M. Ebers (1837-98) published the Ebers Papyrus in two volumes under the title 'The Secret Book Written in Hieratic Script on the Medicines of the Egyptians.' It contains around 250 diseases and 875 prescriptions, explaining medicinal prescriptions and health advice (Bayat, 2016). Useful information about henna is mentioned in these medical texts (Cartwright, 2021).

The health benefits of henna have been addressed in Tibb-i Nabawi. Tibb-i Nabawi is a compilation of the sayings of Prophet Muhammad regarding diet and medical rules, collected by Muslims (Perho, 1995). In Tibb-i Nabawi, it is mentioned that 'the Prophet recommended using henna for skin and dermatological diseases. It is applied on burns, functions as a pain reliever, treats scabies, promotes hair growth, prevents stress, and is used for beautification purposes.' Therefore, for Muslims, henna holds a sacred aspect in this regard. The use of henna burning or applying henna is thus considered a tradition. In Anatolian Folk culture, the knowledge that burning henna is a tradition has been passed down orally within daily life and survived to the present day (Dalan Polat, 2020).

According to Yardımcı (2008), it is known that henna has been used in Turkish medical history for a very long time. Ancient Turks used henna against the plague. In the 16th century, henna pounded with dried grapes was made into a pill and swallowed to relieve phlegm among the public. Also during that period, a paste made by grinding fennel seeds with henna was applied to the temples for headaches. A mixture of watermelon juice, vinegar, and henna was wrapped around the head as a remedy for a cold. Additionally, henna boiled with a small amount of water was applied to the head for eye pain (Ünver, 1938).

Figure 1. Henna (*Lawsonia inermis*) plant (a. Kaynar 2023, b. Anonymous, 2023)

Figure 1 shows the dried, ground and powdered form of the henna plant.

2. MATERIALS AND METHODS

As material in this study; 2.5 Nm wool carpet yarn, 11 Mordant substances; Aliminum sulfate, Copper II sulfate, Ferrous II sulfate, Potassium aluminum sulfate, Potassium bichromate, Tartaric acid, Sodium hydrosulfite, Apple vinegar, Acetic acid, Citric acid, Zinc chloride, city water and Henna (L. inermis) plant were used as liquid.

Firstly, a plant extract was prepared to dye wool yarns. Dry henna plant material was taken in a ratio of 1:1 concerning the wool, placed in a cloth bag in powdered form. It was boiled with water in a ratio of 1:20 concerning the wool until the plant reached the boiling point, then boiled for an additional 60 minutes. Afterward, the plants were allowed to cool in the dyeing vat, and subsequently filtered by straining out the plants. This process is referred to as a hot extract. The second process involves preparing 11 different mordant substances in proportions of 2% and 4% concerning the weight of the wool that will be dyed. Each mordant is individually placed into the dye pots and dissolved in water at 20 times the weight of the wool to be mordanted. The previously soaked wool in cold water is boiled with the mordant substances inside these pots for 60 minutes. The pots are left to cool. Once cooled, the wool is gently squeezed without rinsing, then left to dry. The final step involves dyeing the mordanted wool separately in pots with the prepared plant-based dye extract. Again, water, 20 times the weight of the wool, is taken, and the wool is boiled for 60 minutes. After cooling, the wool taken from the dye pot is thoroughly rinsed with cold water and left to dry.

After the dyeing process is completed, the wools are prepared for light and rub fastness according to standards. Following the application of fastness tests to the samples, a 'blue scale' is used for lightfastness measurement, and a 'Grey Scale' is used for rub fastness.

3. RESULTS

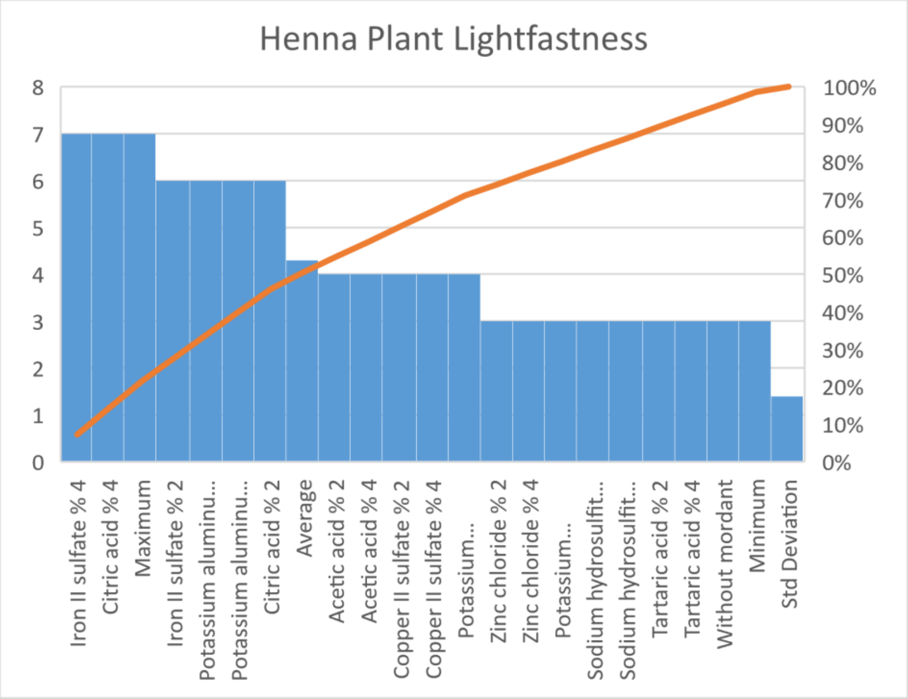
The colors obtained as a result of the dyeing experiments performed with the henna plant are presented in Table 1.

Table1. Color samples obtained from dyeing with henna plant

MORDAN	EXAMPLE	COLOUR
Without mordant		Dark cumin
Aliminum sulfate %2		Cinnamon 1
Aliminum sulfate %4		Cinnamon 2
Copper II sulfate %2		Chestnut Shell 3
Copper II sulfate %4		Chestnut Shell 4
Ferrous II sulfate %2		Roasted coffee beans 1
Ferrous II sulfate %4		Roasted coffee beans 2
Potassium aluminum sulfate %2		Bonito 1
Potassium aluminum sulfate %4		Bonito 2
Potassium bichromate %2		Chestnut Shell 1
Potassium bichromate %4		Dark chestnut Shell 2
Tartaric acid %2		Bonito 2
Tartaric acid %4		Bonito 3
Sodyum Hidrosülfit %2		Cinnamon 1
Sodyum Hidrosülfit %4		Cinnamon 2
Elma Sirkesi %15		Cinnamon 2
Elma Sirkesi %30		Cinnamon 3
Acetic acid %2		Hazelnut shell 1
Acetic acid %4		Hazelnut shell 2
Citric acid %2		Hazelnut shell 3
Citric acid %4		Hazelnut shell 4
Zinc chloride %2		Chocolate milk
Zinc chloride %4		Chocolate

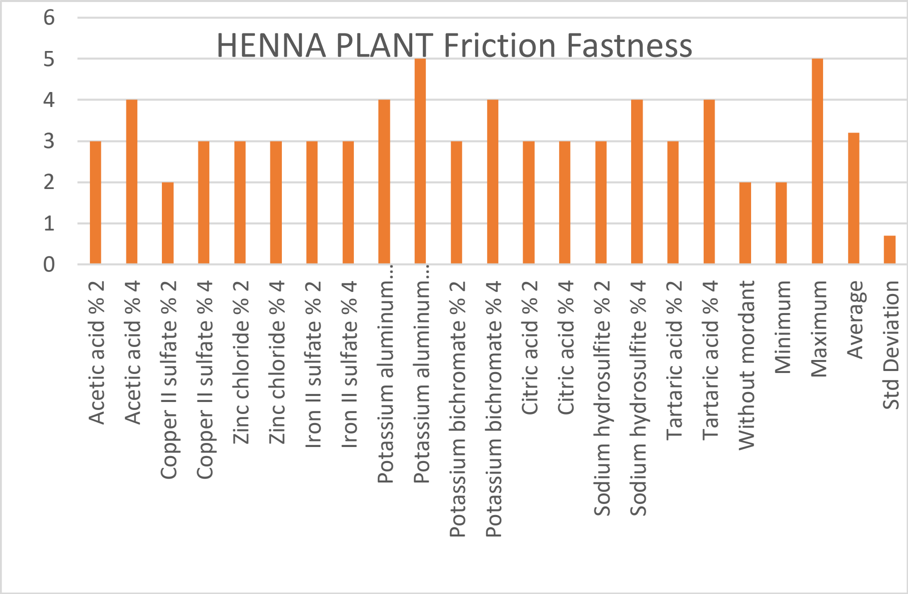
When Table 1 is examined, it is observed that shades of brown and reddish-brown colors such as Dark Cumin, Cinnamon 1-2, Chestnut Shell 1-4, Roasted Coffee Beans 1-2, Bonito 1-4, Dark Chestnut Shell 1-2, Cinnamon 1-3, Hazelnut Shell 1-4, Chocolate Milk, and Chocolate were obtained. The darkest shades were obtained from wool mordanted with Iron II Sulfate, Zinc Chloride, and Copper II Sulfate, while the lightest shades were obtained from dyeing processes carried out using Unmordanted and Potassium Aluminum Sulfate. Quite dark and vibrant colors were achieved.

Table 2. Light fastness of dyeings made with henna plant



When examining Table 2, it is observed that the highest lightfastness values were obtained, respectively, from dyeing processes mordanted with Iron II Sulfate (7), Citric Acid (7), and Potassium Aluminum Sulfate (6). The lowest fastness value was obtained from Zinc Chloride (3), Potassium Bichromate (3), Tartaric Acid, and Unmordanted dyeing (3). It can be said that more than 50% of the dyeing processes exhibit good lightfastness.

Table 3. Friction fastness of dyeings made with henna plant



Rubbing fastness values are given in Table 3. The highest value was obtained from dyeing with Potassium aluminum sulfate (5), and the lowest value was obtained from dyeing without mordant and dyeing with Copper II sulfate (2). The average value was determined as (3).

4. CONCLUSIONS

According to the study by Micahail S. Zavada, the first written sources mentioning the use of henna in Cyprus date back to the periods of Dioscorides and Pliny in the first century AD. According to Pliny and Dioscorides, apart from its medicinal properties, henna in Cyprus also served as a cosmetic agent used in hair dyeing when mixed with soapwort (*Saponaria officinalis*) (Zavada, 1993).

Studies conducted in various countries have observed that naphthoquinone derivatives, such as lawsone found in the composition of henna, exhibit antibacterial and antifungal activities (Polat, 2014; Berenji et al., 2010; Deveoğlu et al., 2011; Abdulyazıd et al., 2013). Furthermore, research conducted on mice has indicated the anti-tumoral activity of henna (Berenji et al., 2010; Zümrütdal & Özarslan 2012). In addition to these findings, henna has been found to possess antioxidant, antidiabetic, tuberculostatic, antitrypanosomal, antifertility, immunomodulatory, nootropic, abortifacient, anticoagulant, analgesic, antiparasitic, antiviral, anti-inflammatory, and hepatoprotective activities.

In this study, a total of 11 mordants were used at 2% and 4% concentrations, namely Aluminum sulfate, Copper II sulfate, Ferrous II sulfate, Potassium aluminum sulfate, Potassium bichromate, Tartaric acid, Sodium hydrosulfite, Apple vinegar, Acetic acid, Citric acid, and Zinc chloride, resulting in 22 mordanted dyeings and one unmordanted dyeing with Henna (Lawsonia inermis) plant. The achieved colors were considerably dark and vibrant such as Dark cumin, Cinnamon, Chestnut Shell, Roasted coffee beans, Bonito, Dark chestnut Shell, Cinnamon, Hazelnut shell, Chocolate milk, and Chocolate. Considering the potential customer preference towards environmentally conscious and green-organic textiles, it is observed that a range of brown and reddish-brown tones, from yellow to brown, representing the colors of nature, are present. This study demonstrates the attainment of colors in brown and reddish-brown tones, which align with customer preferences.

According to research, Henna plant, known for its medicinal properties for various ailments, exhibits results in fabric suitability as indicated by the results obtained from the colorfastness tests, suggesting its potential use in the textile industry.

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CHAPTER 12

USING THE STEMS AND LEAVES OF THE CHERRY PLANT (*Cerasus avium*) WITH SOME TEXTILE FIBERS AS AN ORGANIC DYESTUFF

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DOI: https://dx.doi.org/10.5281/zenodo.10454613

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INTRODUCTION

Some plants' leaves, stems, seeds, bark, roots, among other parts, are used as natural dyes. Historically, when it comes to fruit-bearing plants, mainly their fruit parts have been utilized for consumption, while their other parts have not been considered for dye production. Nowadays, within medicinal and aromatic plants, efforts have begun to explore and utilize all parts of the plants, particularly those remaining parts beyond the fruit, which were previously seen as waste, for various purposes. These plant parts termed as waste have been incorporated into natural dyeing research. In this study, experiments were conducted using cherry stems and leaves to dye wool fibers, although cherries are primarily grown for their fruits intended for consumption

Cherry stems have been the subject of numerous studies in the field of alternative medicine. Cherry stems (CS) are a by-product extensively used as a traditional remedy for urinary tract disorders in Eastern European countries. Ethnopharmacological evidence supports the use of CS in aqueous preparations (infusions and decoctions). However, there has been limited data reported previously on the phytochemical profile and pharmacological potential of CS hydroalcoholic extracts. In this context, a 70% hydroethanolic cherry stem extract and cherry stem decoction (CSD) were evaluated for their phenolic profile, in vitro antioxidant and tyrosinase inhibitory potential, and in vivo diuretic activity. LC-DAD-ESI/MSn revealed the presence of flavonoid-type compounds, particularly flavanones (naringenin glycosides), as the main constituents in both preparations. Overall, our findings indicate the potential use of CS preparations as promising mild diuretic agents and encourage further research on the correlation between their chemical compositions and bioactive potentials (Babota et al., 2021). By-products derived from various plant materials are extensively utilized as promising sources of bioactive nutrients and are considered cost-effective, eco-friendly, and sustainable alternatives compared to standard raw materials (Fierascu et al., 2020).

Additionally, recent studies have revealed the significant accumulation of secondary metabolites in plant residues. For instance, research has shown that a substantial portion of the overall polyphenol content in various food industry residues exists in a form known as non-extractable polyphenols (NEP), which possess noteworthy properties such as antioxidant, antitumor, and hypocholesterolemic effects (Dzah et al., 2020). This suggests that utilizing more by-products as crucial sources of phytochemicals associated with health benefits could be a primary objective in the future (Babota et al., 2021).

Cherry stems (CS) stand as primary residues obtained after the harvesting and processing of cherry fruits. Despite being classified as waste in the food industry, these materials are also used in traditional folk medicine and unconventional therapies (Babota et al., 2021).

Primarily known for their diuretic and soothing properties, the herbal remedy (Cerasorum stipites) is employed (Bastos et al., 2015; Aires et al., 2017; Švarc-Gajić et al., 2018; Nastić et al., 2020; Peixoto et al., 2020).

In Central and Eastern European countries, especially in Romania, based on ethnopharmacological recommendations, cherry stems are commonly utilized as an adjunct in the treatment of kidney stones, mild urinary tract infections, edema, and hypertension. In the Encyclopedia of Romanian Ethnobotany, Butura et al. describe the use of cherry stems as infusions or decoctions in the Carpathian regions for the treatment of kidney disorders. Various traditional decoction recipes involve cherry stems, along with aerial parts of horsetail (*Equisetum arvense*), leaf buds of mountain pine (*Pinus mugo*), and corn stigmas (*Zea mays*) (Butura, 1979).

Moreover, in Romania, among the general population, they are used for their diuretic properties (for cystitis or kidney stones) and also for obesity (Pârvu, 2006).

There have been relatively few phytochemical and pharmacological studies conducted on CS. The majority of available studies in this field have intensified over the last 5 to 10 years, primarily focusing on both qualitative and quantitative evaluations of the main constituents in the extracts and assessing their potential bioactivities. In a comparative study conducted by Bastos et al., (2015) examining the hydrophilic compound profile comparing fruits and stems, they demonstrated the richness of cherry stems in citric, malic, and oxalic acids (Bastos et al., 2015). The same study assessed the phenolic profile of hydroalcoholic extracts obtained from stems, identifying sakuranetin-5-O-glucoside, catechin, naringenin-7-O-glucoside, and aromadendrin-7-O-hexoside as the major components. Other studies revealed the presence of significant amounts of hydroxycinnamic acids (cis-3-O-p-coumaroylquinic acid, chlorogenic acid, and trans-3-O-p-coumaroylquinic acid): quercetin and sinapic acid (Demir et al., 2020; Peixoto et al., 2020). Corroborating the presence of these compounds, various in vitro bioactivities have been evidenced for CS extracts: antioxidant, antitumor, antidiabetic, and antibacterial effects (Bastos et al., 2015; Aires et al., 2017; Demir et al., 2020; Peixoto et al., 2020).

Except for the in vitro antibacterial effect on E. coli strains, only a few studies have focused on evaluating the actual benefits of CS in the treatment of urinary tract disorders (Aires et al., 2017).

In traditional medicine, it's known that cherry stem tea has been used in the treatment of several illnesses. Recently, some health organizations, through publications prepared by Medical Publishing Boards, support the use of natural plant-based sources in alternative medicine and strive to promote their widespread adoption. The benefits of cherry stem and its positive effects on various conditions have been indicated. Cherry stem aids in preventing inflammation in the body, assisting in the cleansing of the kidneys and urinary tract. It reduces the likelihood of infections in the urinary system and decreases edema in the body. Acting as a detoxifier, it facilitates the elimination of toxins. Its potassium content acts as a natural diuretic. It's effective against skin issues like blemishes, acne, and blackheads. It helps prevent the formation of kidney stones. When consumed, it reduces conditions like stress and depression, aids in falling asleep, and shows resistance against body fat and cellulite. Additionally, it plays a role in reducing bloating and pain during menstruation (Anonymous, 2023a).

1. CHERRY PLANT (*Cerasus avium*)

Sweet cherry (*Prunus avium*) trees can grow up to approximately 10 meters if left unpruned, averaging around 5-6 meters. Dwarf varieties (*Cerasus avium*) are considered 'dwarf' when they reach heights of 1.5-2 meters. Cherry trees are deciduous. They can thrive in warm, dry, or semi-arid climates, although they typically prefer cooler climates. They favor deep, well-drained soil enriched with compost and decomposed manure. Protection from direct sunlight and strong winds is advisable. While they can grow in hot and dry climates, they also flourish in shaded areas (Anonymous, 2023b).

Appearance and Characteristics of the Cherry Tree:

The cherry tree is tall and slender. It is a deciduous plant that sheds its leaves in winter and blossoms on bare branches in spring. The leaves emerge after the blossoms. Fruits, on the other hand, ripen in the summer months (Figure 1). Despite growing in the same soil and region, there are species that bloom and bear fruit at different times.

Sweet cherries are the most commonly found variety in markets. They have a thick, rich, and almost plum-like texture. Sweet cherries grow in hardiness zones 5 to 7; they are self-sterile and are best suited for an orchard or large garden. As they need cross-pollination, you will need at least two or three trees. If space is limited, dwarf, self-pollinating 'Stella' cherry tree varieties are planted. They take up less space and ensure pollination. Cherry trees typically do not bear fruit before four years. From a mature, standard-sized sweet cherry tree, you can harvest between 30 to 50 liters of cherries annually. From dwarf cherries, you can yield between 10 to 15 liters of fruit. It's advisable to plant cherry trees in spring or early summer when the soil is softer and has higher moisture content. Apply mulch and water thoroughly. After the fruit blossoms, cover the trees with wildlife-safe nets to protect the fruits from birds. Plant cherry trees in a sunny area with good air circulation; avoid planting them near larger trees or buildings that might shade the cherries. Ideally, cherry trees need at least 6 hours of sunlight daily. Cherry trees thrive in well-drained soil with a pH of 6.0-7.0 (Anonymous, 2023c).

Figure 1. Leaves and fruit of cherry tree (Kaynar, 2020)

In Figure 1, immature fruit, leaves, and fruit stems of the cherry plant are observed.

Cherry trees favor a warm growing season, a period of dormancy during the winter, rainless flowering, and harvest time. Cherries are a type of fruit that requires significant chilling hours; they need over 1000 hours of cold exposure. Irregular flowering and flower shedding occur when this requirement is not met. Approximately 1000 meters in altitude is considered ideal for cultivation. Cherry cultivation should not be practiced in areas where winter temperatures drop below -20 ºC. Excessive summer heat is undesired as it promotes the development of double pistils and, consequently, twin fruits, which lack market value. Cherries prefer soils with low lime content, good drainage, and deep, light texture. The water table should be below 1 meter (Anonymous, 2023d).

The plant contains alkaloids, tannins, saponins, flavonoids, polyphenols, proanthocyanidins, cyanidins, and myoinositol. Additionally, various chemical flavonoid types (flavonones, flavans, biflavonoids) are present. In 100 grams of cherries, there are 76.3 grams of water, 2.1 grams of protein, 2.3 grams of fat, 17.9 grams of carbohydrates, 4.6 grams of fiber, 1.4 grams of ash, 125 mg of calcium, 94 mg of phosphorus, 0.015 mg of vitamin A, 90 mg of vitamin C, and 380 kj/100 g of energy (Nurfitria et al., 2020, Anonymous, 2023e). In addition to these components, cherry plants also contain trichome cells. Secondary plant formation Metabolites are found in all tissues and cells, but biosynthesis occurs in specific tissues or cells, influenced by differentiation and developmental levels. In the structure of cherry leaves, there are glands that produce sap-containing juice and secrete wax when touched (Kuntorini et al., 2013).

2. MATERIAL METHOD

The materials used included dried cherry plant leaves, fruit leaves, 2.5 Nm wool carpet yarn, and 9 types of mordant substances: aluminum sulfate, acetic acid, copper II sulfate, iron II sulfate, citric acid, potassium alum. sulfate, potassium bichromate, zinc chloride, and tartaric acid. To prepare the plant extraction, 1000 grams of dry plant leaves and cherry husks were mixed in equal proportions. Initially, they were placed in 20 liters of water at room temperature and boiled until reaching the boiling point. Subsequently, the mixture was stirred at the same temperature for approximately one hour. Afterwards, the plant residues were removed from the boiling water and left to cool. Wool carpet yarns were prepared with mordant substances at 2% and 4% ratios, mixed with water, and boiled for one hour. The resulting mordanted wool was individually boiled with the previously prepared plant extract. Once cooled, the yarns were rinsed with cold water, dried, and obtained as dyed wool yarns.

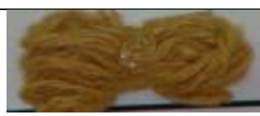
3. RESULTS

Color samples obtained from dyeing with cherry plant leaves and stems and the names given to these colors are given in Table 1.

Table:1 Color samples obtained from dyeing with cherry plant leaves and stems

MORDAN	EXAMPLE	COLOUR
Aliminum sulfate %2		Cumin 1
Aliminum sulfate %4		Cumin 2
Acetic acid %2		Mustard 1
Acetic acid %4		Mustard 2
Copper II sulfate %2		Cinnamon 1
Copper II sulfate %4		Cinnamon 2
Ferrous II sulfate %2		Roasted coffee beans 1
Ferrous II sulfate %4		Roasted coffee beans 2
Zinc chloride %2		Melon 1
Zinc chloride %4		Melon 2

Table 1. (continued)

MORDAN	EXAMPLE	COLOUR
Potassium aluminum sulfate %2		Mustard 2
Potassium aluminum sulfate %4		Mustardl 3
Potassium bichromate %2		Hazelnut shell 1
Potassium bichromate %4		Hazelnut shell 2
Citric acid %2		Coffee foam 1
Citric acid %4		Coffee foam 2
Tartaric acid %2		Coffee foam 3
Tartaric acid %4		Coffee foam 3
Without mordant		Wheat stalk

In this study, using nine mordant substances Citric acid, Aluminum sulfate, Acetic acid, Copper II sulfate, Iron II sulfate, Zinc chloride, Potassium aluminum sulfate, Potassium bichromate and Tartaric acidshades of yellow, orange, and brown were obtained. These colors were named as follows: Cumin 1-2, Mustard 1-2-3, Cinnamon 1-2, Roasted coffee beans 1-2, Clove 1-2, Walnut shell 1-2, Coffee froth 1-2-3.abundance of cherries in the country, very few people are aware of the useful leaves containing flavonoids and tannins for textile dyeing. The eco-print dyeing process using Jamaican cherry leaves (*Muntingia calabura*) involved steam fixation techniques for coloration analysis. The study was conducted through an eco-print dyeing experiment, followed by laboratory tests to examine color variations. Middle-aged cherry leaves were selected and steamed for dyeing purposes. Iron (iron sulfate), alum, and calcium carbonate were used as mordants to fix the colors. The steaming process was conducted twice, each lasting 30 minutes. Each fabric was immersed in the mordant solution for 5-10 minutes to facilitate fixation. Dyeing with cherry leaves using alum as a mordant resulted in brownish-yellow, with iron; black-green, and with calcium carbonate; brownish-green colors (Nurfitria et al., 2020). It was observed that the nine types of mordants used in this research showed similarities in color tones obtained in the dyeing process without mordants.

4. CONCLUSIONS

In this study, using nine mordant substances-Aluminum sulfate, Acetic acid, Copper II sulfate, Iron II sulfate, Zinc chloride, Potassium aluminum sulfate, Potassium bichromate, Citric acid, and Tartaric acid-shades of yellow, orange, and brown were obtained. Consequently, it's observed that mordant substances influenced the hue and intensity of the dyeing process. Similarities can be drawn with the study conducted in Indonesia. The cherry plant is extensively cultivated in our country, and its fruit is widely utilized. The darkest shade was obtained from a dyeing process utilizing Iron II sulfate as the mordant. Successively, the deepest tones were achieved from samples dyed with Copper II sulfate and Potassium dichromate as mordants. It is important to note that while Potassium dichromate resulted in the desired depth of color, it is not recommended for use in items that come into contact with human skin due to health concerns. The lightest shade, wheat straw yellow, was determined from dyeing conducted without any mordant used. Medium-depth colors were obtained with other mordantsRecently, cherry stems have been included among medicinal organic plants, and as seen in various studies, their use in alternative medicine has begun to increase, especially as diuretics, antioxidants, and anti-inflammatory agents. According to the results obtained in this research, dyeing with parts of the cherry plant other than the fruit could be applied in eco-friendly textile production and could serve as inspiration for further investigation.

Dyeing with mixtures of minimal mordant substances along with cherry plant leaves and stems can yield functional benefits and original colors. Additionally, it is suggested that apart from the plant's stems and leaves, its bark, buds, and flowers can also be used as dye materials. Furthermore, its lack of synthetic solvents is predicted to increase demand, primarily for baby and children's products, leading to the use of all-natural fibers, resulting in sustainable outcomes.

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CHAPTER 13

LEGUME FORAGE CROPS WITH MEDICINAL VALUE AND THEIR SECONDARY METABOLITE CONTENTS: *Astragalus* sp., *Crotalaria* sp., *Lespedeza* sp., *Lotus* sp.

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DOI: https://dx.doi.org/10.5281/zenodo.10454622

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INTRODUCTION

Legume forage plants are rich in vitamins, minerals and proteins and are important feed sources for animal nutrition and critical components of natural and agricultural ecosystems. At the same time, forage legumes are a source of various antinutrient compounds, also known as bioactive compounds. These compounds are also produced to improve the resistance mechanisms of forage plant species to various environmental stress conditions. However, the content of secondary metabolites may affect the health of grazing animals and the possible use of plants in pharmacology. In turn, they can exhibit a wide range of bioactivities that are beneficial to human health, such as anticarcinogenic, anti-allergenic, antioxidant, anti-inflammatory, antimicrobial, anti-cancer and analgesic activities.

The qualities of plant secondary metabolites as a new source of natural antioxidants and the activities they exhibit have recently become the focus of research in this field. In this chapter, the secondary metabolites contained by various plant species belonging to the *Astragalus* sp., *Crotalaria* sp., *Lespedeza* sp., and *Lotus* sp. genera, which are important in legume forage culture, and the medicinal values of these compounds are focused on.

1. *Astragalus* sp. (*Astragalus* L.)

Astragalus L. is one of the largest flowering plant genera of the Leguminosae family; it includes annual or perennial plant species in subshrubs or shrubs form that commonly grow in arid regions (Miraj and Kiani, 2016). The genus *Astragalus* is a large genus represented by 10 subgenera, 130-136 sections and 2438-3270 species (Maassoumi, 1998; Rundel et al., 2015). There are 20 endemic species of *Astragalus* in Türkiye (Kızıltaş et al., 2021). The species it contains are a rich source of protein, fat, carbohydrates, vitamins and microelements, and its herbs and seeds have high nutritional value. Moreover, the *Astragalus* genus are sources of various secondary compounds with antioxidant properties, including phenolic acids and flavonoid compounds. Therefore, plants of the genus *Astragalus* are of great importance for medicinal applications.

The pharmacologically active components of the *Astragalus* genus are polysaccharides, saponins and flavonoids (Rios and Waterman, 1997; Ma et al., 2002; Mehraban et al., 2014). Among these, flavonoids represent the largest group of polyphenolic compounds occurring in *Astragalus* species. In this sense, many different flavonoid subclasses have been identified from the genus *Astragalus*, such as flavones, flavonols, flavanones, flavanonols, chalcones, aurones, isoflavones, isoflavanes, and pterocarpans (Bratkov et al., 2016). Flavonols are the most frequently isolated compounds and among these, quercetin, kaempferol, and their glycosides were found in a larger number of *Astragalus* species (Bratkov et al., 2016). In addition, some toxic compounds such as indolizidine alkaloids, aliphatic nitro compounds and seleniferous derivatives have also been identified (Rios and Waterman, 1997; Pistelli, 2002; Mehraban et al., 2014). Krasteva et al.

(2000) reported that Astraciceran was the first isoflavan isolated from *A. cicer*.

Astragalus cicer L. and *A. glycyphyllos* L. species have the potential to be a source of phenolic substances, isofavones and free radical scavengers, and have antioxidant properties. Secondary metabolites and antioxidant properties in these species vary depending on the species, plant growth stage and plant parts. In this sense, these species can be considered as a potential source for dietary supplements and pharmaceutical and nutraceutical products (Butkutė et al., 2018). *Astragalus tenuifoliosus* seeds were found to have significant antioxidant activities, high flavonoids and phytochemical content, and 8 phenolic acids and 10 flavonoids were characterized. For this species, quinic acid, p-coumaric acid, trans-ferulic acid, quercetin and cirsiliol were identified as the main phenolics. In this manner, *Astragalus* seeds have been promising for use as a new source of natural antioxidants and bioactive compounds (Mahmoudi et al., 2023).

A type of sapogenin in *A. angustifolius* (Nikolov et al., 1985) and *A. glycyphyllos* (Elenga et al., 1987), complanatin-a new rhamnocitrin glycoside in *A. complanatus* seeds (Cui et al., 1991), flavonol tetraglycoside in *A. caprinus* (Semmar et al., 2001), two flavanone glycosides in *A. corniculatus* and *A. ponticus* (Krasteva et al., 2004a; Krasteva, 2013), saponins in *A. corniculatus* (Krasteva et al., 2006, 2007), sulfuretin, the only aurone isolated from this genus in *A. microcephalus* (Alaniya et al., 2009), flavonol tetraglycosides in the leaves and flowers of *A. falcatus* (Alaniya et al., 2011), tamarixetin triglycoside in the aerial parts of *A. armatus* (Khalfallah et al., 2011), and C-glycoside, a new flavone, in *A. bombycinus* (Ibrahim et al., 2013) have been identified. In addition, isoflavans were determined in *A. alexandrinus* and *A. trigonus* species (El-Sebakhy et al., 1994), and isoflavone was determined in *A. peregrinus* species (Abd El-Latif et al., 2003).

Astragalus species have been known to have medicinal properties for thousands of years (Krasteva et al., 2016). *Astragalus* spp. has long been used as medicinal plants in folk medicine as cardiovascular, antihypertensive, diuretic, choleretic, antimicrobial and antiviral agents. Plants of the genus exhibit a wide range of pharmacological effects, among which diuretic, anti-inflammatory, bactericidal, hypotensive, and sedative effects are important (Lysiuk and Darmohray, 2016). Furthermore, *Astragalus* L. genus has anti-inflammatory, immunostimulant, antioxidative, anti-cancer, antidiabetic, cardioprotective, hepatoprotective, and antiviral activities (Li et al., 2014). Clinical studies have shown that *Astragalus* polysaccharides can increase the effectiveness of platinum-based chemotherapy (McCulloch et al., 2006), improve the quality of life of advanced non-small cell lung cancer patients (Guo et al., 2012), and mediate the antitumor effect (Wu et al., 2017). For this reason, *Astragalus* is recommended in traditional Chinese medicine for the treatment of cancer (Block and Mead, 2003; Zheng et al., 2019). In this sense, the immunomodulatory and anti-cancer activities of various species belonging to the genus *Astragalus* have been reported in numerous studies (Wang et al., 2015; Zhu et al., 2015; Zhou et al., 2018a, 2018b; Li et al., 2020; Mehraban et al., 2020).

The leaves, roots and stems of *Astragalus membranaceus*, an important member of this genus, have been reported to have anti-cancer and tumor activities and high anti-carcinoma activities such as lung, colorectal, breast, ovarian, liver, colorectal, stomach, colon, gastric, cervical, nasopharyngeal (Miraj and Kiani, 2016). Additionally, Auyeung et al. (2010) stated that *A. membranaceus* has potential antitumorigenic effects; Lekmine et al. (2020) reported that *A. gombiformis* is an important source of natural anti-diabetic, antioxidants and anti-Alzheimer's disease.

Krasteva et al. (2016) reported that the main biologically active compounds found in Bulgarian *Astragalus* plants are saponins and flavonoids; they have various effects such as immunomodulatory, hepatoprotective, cytotoxic, antioxidant, antihypoxic. Bratkov et al. (2016) provided information about the anti-oxidant, radioprotective, hepatoprotective, antifibrotic, antimicrobial, cytotoxic, antidiabetic, anti-inflammatory activities of *Astragalus* species and their biological activities on the cardiovascular system, respiratory system, nervous system and urinary system.

A purified mixture containing saponins from *Astragalus corniculatus* has been shown to have a protective effect against Graffi myeloid tumor in hamsters; it was determined that the survival rate and duration increased and tumor growth decreased significantly after application (Krasteva et al., 2004b).

Another species, radix astragali (*A. mongholicus*), is a well-known medicine of traditional medicine used in the treatment of general debility, chronic diseases, to increase the general vitality of the human body, in cases of diarrhea, fatigue, loss of appetite and night sweats (Sinclair, 1998). *Astragalus gombiformis* has traditionally been used to treat snake and scorpion bites (El Rhaffari and Zaid, 2002).

Besides, *A. centralpinus* has spasmolytic activity (Paskov and Marechkova, 1983), *A. quisqualis* and *A. floccosifolius* has antiulcer activity (Barnaulov et al., 1985), *A. membranaceus* has protective activity against liver damage (Shen et al., 1997), antihypoxic activity of *A. corniculatus* (Krasteva et al., 2004a) and immunoregulatory effect of *A. membranaceus* (Kuo et al., 2009) were detected.

As a result of a study aimed at determining the chemical profile and some biological activities of three endemic *Astragalus* species in Anatolia, it has been reported that the flavonoids most commonly found in *A. leporinus* var. *hirsutus*, *A. distinctissimus* and *Astragalus schizopterus* species were rutin and hesperidin, as well as quinic acid and palmitic acid have been identified as the main compounds. Moreover in the research, high cytotoxic effect of *A. leporinus* var. *hirsutus* and high antioxidant activity of *A. schizopterus* were identified. Researchers have stated that these *Astragalus* species used as animal feed may be the source of natural, biologically active agents that can be used in the food and pharmaceutical industries (Haşimi et al., 2017).

In addition to all these, it has been emphasized that the toxic compounds contained in some species of *Astragalus* can pass to humans through milk and meat in many cases (Rios and Waterman, 1997).

It can be said that the *Astragalus* genus, consisting of approximately 3000 species, is a valuable source of herbal medicine. This great breed attracts attention not only as a roughage source, but also as a source of secondary metabolite diversity and the resulting pharmacological effect.

2. *Crotalaria* sp. (*Crotalaria* L.)

The genus *Crotalaria*, located in the Fabaceae family, has approximately 600-700 species, mostly distributed in the tropical and subtropical regions of the southern hemisphere and Africa (Lewis, 2005; Mosjidis and Wang, 2011; Devendra et al., 2012). *Crotalaria juncea* Linn., the most important member of this genus, is a native plant of Asia, especially tropical Asia (Bangladesh, Bhutan, India) (Al-Snafi, 2016). *Crotalaria juncea* has also been recorded in many countries on the African continent, from the Atlantic coast to the Red Sea, from Tunisia to South Africa and the islands of the Indian Ocean (Maroyi, 2011; Anonymous, 2023). Apart from *C. juncea*, there are also important *Crotalaria* species such as *C. retusa* L., *C. spectabilis* Roth., *C. burhia* Buch.-Ham. and *C. pallida* Aiton; these species are mostly grown for fiber, green manure and soil protection (Pandey et al., 2010). Additionally, there are other species such as *C. laburnifolia* L., *C. nana* Burm f. and *C. verrucosa* L. that have the potential to be used in land reclamation, as ornamental plants and as medicinal plants (Satya et al., 2016). Plants belonging to the *Crotalaria* genus are most commonly used as green manure plants (Daimon, 2006).

Crotalaria juncea is popularly known as sunn hemp and is used by ethnic communities for its food, fiber and medicinal values (Chouhan et al., 2011). The nutritional quality of its seeds is high and the plant is also used as fodder and green manure plant (Rawat and Saini, 2022). In addition to this bio oil obtained from *C. juncea* seed has been reported as a promising new source for biofuel production (Dutta et al., 2014). Although *C. juncea* is rich in many nutrients, the presence of anti-nutritional factors limits its use in food (Rawat and Saini, 2022).

Secondary metabolites isolated from various species of the *Crotalaria* genus constitute the alkaloid, pyrrolizidine alkaloid, phytosterol, pterocarpanoid, steroidoid, polyketoid flavonoide, isoflavan flavonoid, steroid saponin, flavonoid, flavone glycoside, chalcone flavonoid, sterol, steroid and chalcone group (Yaqub et al., 2020). As a result of the phytochemical analysis of leaves and seeds of *C. juncea*, the most important species of the genus, the presence of carbohydrates, steroids, triterpenes, phenolics, flavonoids, alkaloids, amino acids, saponins, glycosides, tannins and essential oils were revealed (Chouhan and Singh, 2010; Al-Snafi, 2016). Anwar et al. (2022) reported that in the analysis of methanolic extracts of the *C. burhia* Buch.-Ham. species, important secondary metabolites such as polyphenols, saponins, flavonoids, and glycoside derivatives were tentatively identified, and that this plant can be considered a promising source of bioactive compounds with various therapeutic uses. Some other researchers have reported the presence of triterpenoids, flavonoids, anthraquinones, phenols, polyphenols, steroids, alkaloids, and tannins in the same plant (Kataria et al., 2011; Kumar et al., 2011; Bibi et al., 2015). In general, the main secondary metabolite group of the *Crotalaria* genus consists of alkaloids, flavonoids, saponins and steroids.

Crotalaria juncea is used as a blood purifier, abortifacient, demulcent, purgative and in the treatment of anaemia, impetigo, menorrhagia and psoriasis (Kirtikar and Basu, 1935; Chopra et al., 1956; Sharma et al., 2001). Vijaykumar et al. (2003) reported that various parts of *C. juncea* were used in Indian Ayurvedic Medicine for their properties such as analgesic, astringent, emmenagogue, abortifacient and also treatment of skin diseases. Anti-obesity, antitumor and anti-diarrhea properties of *C. juncea* have also been demonstrated (Lalitha et al., 2011). In studies conducted with *C. juncea*; anti-hypercholesteraemic effects of ethanolic extracts of whole plant parts (Bremekamp, 1944), methylene chloride and methanol extracts of the aerial part have moderate antifungal properties (Goun et al., 2003), anti-inflammatory and anti-ulcerogenic properties of ethanol extract of leaves (Ashok et al., 2006), the seed is antibacterial (Chouhan and Singh, 2010), seed oil has important antioxidant and anti-inflammatory properties (Moylan et al., 2004; Chouhan et al., 2011) and antibacterial (Moylan et al., 2004), antihyperlipidemic and antihyperglycemic of the ethanolic extract (Rajesh et al., 2014) has been reported to have activity.

The ethanolic extract of *C. juncea* affected various blood lipids and metabolic parameters in rats; this has been shown to provide potential benefit as an antihypercholesterolemic agent (Sathis Kumar et al., 2014). Additionally, *C. juncea* seed extract has been proven to have hepatoprotective power (Rahila et al., 2013). Al-Snafi (2016) reported that *C. juncea* has hypolipidemic, reproductive, antioxidant, antibacterial, antifungal, anti-diarrheal, anti-inflammatory, hepatoprotective and many other pharmacological effects.

Crotalaria quinquefolia L., another *Crotalaria* species, is used in folklore medicine to treat fever, pain, eczema, impetigo, lung infections and scabies (Jahan et al., 2019); the roots and seeds of *C. pallida* are used in the treatment of scrofula, dysentery neurasthenia and tumors (Hu et al., 2017). Nahar et al. (2024) reported in their research that *C. quinquefolia* extract has anti-diabetic activity. Another species, *Crotalaria burhia,* is a very important medicinal plant used in the treatment of different ailments (Anwar et al., 2022). Anwar et al. (2022) reported that the leaves, roots and branches of *C. burhia* have anticancer and soothing properties, fresh plant juice can be used to treat eczema, goût, hydrophobia, pain, and edema, sugary root extract is used to relieve chronic kidney pain and treat typhoid fever. In another study, it was reported that the methanolic extract of the whole plant part of *C. burhia* had significant antinociceptive and anti-inflammatory (Kataria et al., 2012), and the methanolic extract of the root had antitumor and antioxidant activities (Talaviya et al., 2018).

In some other species of *Crotalaria*, e.g. *Crotalaria pallida* anti-diabetic (Panda et al., 2015), *Crotalaria retusa* antioxidant (Blois, 1958; Anim et al., 2016), *Crotalaria verrucosa* anti-diabetic (Nawrin et al., 2015), antibacterial (Prasad et al., 2015), antipyretic and thrombolytic (Nawrin et al., 2015), hepatoprotective (Lekharani et al., 2013), *Crotalaria madurensis* anti-oxidant (Hala et al., 2008), *Crotalaria ferruginea* anti-cancer (Saeidnia et al., 2014), *Crotalaria sessiliflora* anti-oxidant (Munim et al., 2003) and anti-tumor (Liang et al., 1980) such as pharmacological activities have been observed.

Considering that many species of the *Crotalaria* genus have not yet been scientifically investigated (Anwar et al., 2022), it is important to conduct biochemical and biological analyzes of *Crotalaria*-specific compounds and make more use of *Crotalaria*. Considering the secondary metabolites they contain, it would be appropriate to conduct further research to protect and genetically improve the genetic resources of species belonging to this large genus of the legume family.

3. *Lespedeza* sp.

There are three important types of *Lespedeza* genus (Leguminosae): *Lespedeza cuneata* (Dum. Cours.) G. Don., *Lespedeza bicolor* Turcz. and *Lespedeza davurica* (Lax.) Schindl. *Lespedeza cuneata* is a warm-season perennial legume plant that grows in a variety of habitats such as prairies, woodlands, and swamps, and even in high drought and shade conditions (Hu et al., 2014). *Lespedeza bicolor* is a shrub-shaped legume that can adapt to acidic, infertile soils and plays an important role in forage production and soil protection (Dong et al., 2008). This plant is also grown for ornamental purposes all over Asia (Lee et al., 2016); it also has the capacity to increase soil fertility through symbiotic nitrogen fixation, and with this feature it is used for land reclamation

(Li et al., 2004). *Lespedeza davurica* is a valuable feed thanks to its tolerance to extreme cold and drought and its high nutritional value (Zhao et al., 2022). In addition to this, it is a natural pasture type with high adaptability (Xu et al., 2011).

Phytochemical analysis of *L. cuneata* revealed the presence of various types of compounds such as lignans, phenylpropanoids, pinitols, flavonoids, and tannins (Matsuura et al., 1978). As a result of another research, β-Sitosterol, succinic acid, triacontan-1-ol, quercetin, kaempferol, pinitol, avicuralin, juglanin and trifolin were isolated from the leaves of *L. cuneata* and their structures were determined (Shin et al., 1978). Degen et al. (1995) reported that condensed tannins are common in the *L. cuneata* species and Mariadoss et al. (2023) reported that phytochemical analysis showed that *L. cuneata* has a rich source of favonoids, pinitols, phenylpropanoids, sterols, tannins, triterpenoids, lignins, etc. Twelve flavonoids, including quercetin, kaempferol, trifolin, isoquercetin, homoorientin, and orientin, have been isolated from *Lespedeza bicolor* (Glyzin et al., 1970). In another research, various compounds such as ethyl caffeate, caffeic acid, betulinic acid, betulin, b-sitosterol, protocatechuic acid, genistein, quercetin, daidzein, catechin, routine, luteolin, naringin, and isoflavanones were identified in *Lespedeza bicolor* (Maximov et al., 2004; Tan et al., 2007). *Lespedeza davurica* is a rich source of flavonoids and polyphenols and contains kaempferol, tamarixetin, leteolin, quercetin, epicatechin, triofolin, routine, and contains some phenolic compounds (Xu et al., 2010). In a different study, six compounds including kaempferol, quercetin, kaempferol 3-O-β-D-glucopyranoside, rutin, vanillic acid and β-sitosterol were isolated from the aerial parts of the *L. davurica* plant (Weng et al., 2012). Besides, many bioactive compounds including flavonoids, D-fructose, D-pinitol, sterols, and catechins have been isolated from different *Lespedeza* species (Deng et al., 2007).

Lespedeza has been used to treat and prevent diabetes since ancient times in South Korea (Zhou et al., 2011). *Lespedeza cuneata* is used in traditional medicine to treat diabetes, hematuria and insomnia, and bioactive compounds obtained from *L. cuneata* have various pharmacological properties (Baek et al., 2018). It has been reported that *L. cuneata* extracts have hepatoprotective (Kim et al., 2016), antidiabetic (Sharma et al., 2014; Kim et al., 2016; Mariadoss et al., 2023), anti-hyperlipidemic (Mariadoss et al., 2023) effects, anticancer and antioxidative activity, inhibitory effects on cell proliferation (Baek et al., 2018), and protective effects against testicular and ovarian diseases (Park et al., 2018, 2019).

Lee et al. (2020) reported that *L. cuneata* extract can be considered an excellent candidate for the herbal treatment of breast cancer. Moreover, *L. cuneata* extracts have beneficial cosmetic effects such as anti-wrinkle, antimelanogenic, anti-aging and anti-oxidative effects (Seong et al., 2017; Lee et al., 2018). Additionally, Kim and Kim (2010) demonstrated that *L. cuneata* has the potential to develop beneficial natural antioxidants. Yoo et al. (2015) suggested that *L. cuneata* and its flavonoid components are candidates for the treatment of various inflammatory diseases. Lee et al. (2019), reported that *L. cuneata* plant material extract was used in folk medicine to treat severe chronic cough, abscess, asthma and eye disorders.

Lespedeza bicolor has been used traditionally in Asia to treat inflammation (Kim et al., 2019). Lee et al. (2016), stated that *L. bicolor* extract has anti-inflammatory, antioxidant activities and tyrosinase inhibitory effects and can be used in the treatment of post-inflammatory pigmentation. Ullah et al. (2012) and Ullah (2017), suggested that the methanolic extract of *L. bicolor* could be a potential candidate for natural antioxidants and anticancer. Do and Lee (2019), reported that *L. bicolor* alleviated diabetic kidney damage. Kim et al. (2019), reported that the natural phyto-constituents rich in *L. bicolor* extract have antioxidant effects, reduce blood sugar level and anti-inflammatory activity, and that *L. bicolor* has the potential to prevent or improve diabetic complications due to hyperglycemia. Tarbeeva et al. (2019) found that some polyphenolic compounds obtained from *L. bicolor* root bark had moderate cytotoxic activity against cancer cells. Ren et al. (2023) determined that honey produced from *Lespedeza bicolor* has medicinal value, 12 polyphenol compounds were identified in *L. bicolor* honey, and the research results determined that *L. bicolor* honey has excellent antioxidant and anti-inflammatory activities. In some studies conducted with *L. bicolor*, its antioxidant activity was also investigated and it was shown to be promising for the treatment of endothelial dysfunction (Lee and Jhoo, 2012; Guo et al., 2020).

Another species of *Lespedeza*, *Lespedeza davurica*, is recommended by Korean traditional healers and this species is used for the treatment of diabetic patients (Sharma and Rhyu, 2015). Sharma and Rhyu (2015) stated that *L. davurica* extract could protect pancreatic β-cell damage and regulate blood sugar. Wu et al. (2009) drew attention that *L. davurica* flavonoids have significant antioxidant activity and pointed out the pharmaceutical value of this species.

4. *Lotus* sp. (*Lotus* L.)

Lotus L. (Fabaceae), which belongs to the Mediterranean Region, New Zealand and North America, includes many species (Girardi et al., 2014; Uzun et al., 2016). The most commonly cultivated species in the world is birdsfoot trefoil (*Lotus corniculatus* L.); other main species are narrow-leaf birdsfoot trefoil (*Lotus tenuis* Waldst & Kit), great trefoil or major trefoil (*Lotus pedunculatus* Cav; syn.: *Lotus uliginosus* Schkuhr) and annual birdsfoot trefoil (*Lotus subbiflorus* Lag) (Girardi et al., 2014). Birdsfoot trefoil which has the ability to grow in harsh environments (low-fertility, acidic, and high-salinity soils) and is rich in secondary metabolites is considered an important forage plant and medicinal plant worldwide (Wang et al., 2013). The plant attracts attention with its amount of flavonoids, which include a wide group of polyphenolic compounds among secondary metabolites. Although the plant is a single species, it differs greatly from its sub-variety, *Lotus corniculatus* var. *japonicus*, in terms of the amount and distribution pattern of flavonoids (Wang et al., 2013). Besides, Jones (1968, 1970) cyanogenic glycosides of *Lotus corniculatus*, Jones et al. (1973) and Degen et al. (1995) reported that it produced condensed tannins. Foo et al. (1996) detected compounds such as epicatechin, epigallocatechin, epiafzelechin and catechin in birdsfoot trefoil. In *Lotus* species, Reynaud and Lussignol (2005) pointed out the existence of flavonoids such as quercetin ve kaempferol, Moro et al. (2010) pointed out of the existence rutin and vitexin, El Mousallami et al. (2002) and Khalighi-Sigaroodi et al. (2012) pointed out the presence of proanthocyanidins, tannines, flavonoids, oleanolic acid, and saponins. Kaducová et al. (2022) report that kaempferol glycosides are the dominant flavonol compounds in the leaves of *Lotus corniculatus*. Some other studies conducted with the *Lotus* genus have similarly revealed the presence of flavonoids, saponins, phenolic acids, coumarins, sterols, sugars and various compounds (Golea et al., 2012; Araniti et al., 2014; Zhao et al., 2019). Additionally, one of the most important chemical components of *Lotus corniculatus* is oleanolic acid (El-Gazzar et al., 2022).

The high flavonoid content in *Lotus corniculatus* makes it an ideal ingredient for animal feed as it improves digestion and reduces bloating (Sivakumaran et al., 2006). Many flavonoid compounds play an important role in protecting against various biotic and abiotic stresses (Dixon et al., 2002; Treutter, 2005) and in mediating pollination with their attractive properties such as color and smell (Özyazıcı, 2023a). In addition to this, more importantly, they can be beneficial to human health (Wang et al., 2013). Because many flavonoid compounds are active components of medicinal plants and exhibit pharmacological effects such as antioxidant, anticancer and anti-inflammatory properties (Özyazıcı, 2022, 2023b). The aerial parts of *Lotus corniculatus* which is a traditional Turkish medicinal plant, are used as painkiller, antihemorrhoidal, diuretic and sedative (Altundag and Ozturk, 2011). *Lotus corniculatus* is traditionally used in Persian folk medicine to treat various types of pain, such as peritoneal inflammation, migraine, toothache, and back pain (Baali et al., 2020; Jabbari et al., 2024).

Koelzer et al. (2009) reported that *Lotus corniculatus* shows important anti-inflammatory activity by inhibiting not only leukocytes and/or exudation but also pro-inflammatory enzymes and mediators like myeloperoxidase, adenosine-deaminase and interleukin-1 beta.

They reported that secondary metabolites present in *Lotus* species have potential uses in the treatment of peptic ulcers and sexually transmitted diseases and as antioxidants and anticancer agents (El Mousallami et al., 2002; Khalighi-Sigaroodi et al., 2012). In a study conducted to determine the antioxidant capacity of *Lotus corniculatus*, important bioactive substances such as tannins, saponins, glycosides, gallic acid, phenolic (coumarin, catechin) and flavonoids (kaempferol, quercetin, routine, quercitrin, naringenin, naringin) have been found in the stem, leaves and seeds of this species and it has been emphasized that the plant can be used as a potential source of compounds with antioxidant properties in cosmetics, pharmacy and food industries (Abdel-Alim et al., 2023).

Gürağaç Dereli et al. (2020) reported that the extract of the aerial parts of *Lotus corniculatus* subsp. *corniculatus* showed antidepressant activity, and that this effect was probably due to flavonoids. Researchers emphasized that further studies should be conducted on the mechanism of these compounds to develop new antidepressant drugs.

Various biological activities have been reported for *Lotus corniculatus*, such as anticancer (Aissaoui et al., 2014), antioxidant, trypanocidal, immunostimulatory and antiprotozoal activities (Abdallah et al., 2021), and analgesic activity against nociceptive and neuropathic pain conditions (Jabbari et al., 2024). In some other studies conducted with *Lotus* species, for example; *Lotus lalambensis* has excellent anti-inflammatory effects against inflammation (El-Youssef et al., 2008), *Lotus polyphyllos* has hepatoprotective activity (Osman et al., 2013), and *Lotus edulis* has anticancer effects (Tselepi et al., 2011) reported. As a result of a study conducted with another member of the *Lotus* genus (Youssef et al., 2020), *Lotus arabicus* may have active components that can be used in the treatment of prostate, colon or lung cancer; therefore, it has been reported that there may be a need to isolate phenolic and flavonoid compounds found in *Lotus arabicus* in the future.

5. CONCLUSIONS

Astragalus sp., *Crotalaria* sp., *Lespedeza* sp. and *Lotus* sp. legume forage plant species, which are among the important forage sources in animal nutrition, are among the most important instruments of traditional medicine due to the wide variety of secondary metabolites they contain. These plant species, which have been used in traditional medicine for thousands of years, have also attracted the attention of the pharmaceutical industry in recent years. Based on the results of this review, it can be concluded that the mentioned species have convincing medicinal potential. Therefore, identifying secondary metabolites from the Astragalus, Crotalaria, Lespedeza and Lotus genera and revealing their activities may provide new opportunities for the widespread use of species belonging to these genera.

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CHAPTER 14

THE SECONDARY METABOLITE CONTENT AND MEDICINAL VALUE OF SORGHUM (*Sorghum* sp.) SPECIES

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DOI: https://dx.doi.org/10.5281/zenodo.10454630

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INTRODUCTION

Sorghum varieties, which are among the most important cereal crops in tropical and subtropical semi-arid regions worldwide, play a crucial role in ensuring global food security (Monk et al., 2014; Xu, 2019). Classified in the Poaceae (Gramineae) family, sorghum belongs to the *Sorghum* genus and is a plant native to Ethiopia (Spangler et al., 1999; Dillon et al., 2007). Sorghum is widely utilized as a food source for human consumption, fodder for animal feed, and a plant for food, fiber, and bioenergy. In addition to its use as a source of food and feed, sorghum is employed as a raw material for various purposes such as stem and fiber source, construction material, fencing material, fuel, and more recently, as a raw material for cellulosic ethanol (House, 1985; Doggett, 1988; Rooney and Waniska, 2000; Wang et al., 2016). Sorghum grain is a staple food for nearly 500 million people in approximately 30 countries in Asia and Africa. Despite making a significant contribution to global food production, the majority of sorghum grain in Western countries is primarily utilized as animal feed (Proietti et al., 2015; Khoddami et al., 2023). Sorghum is used in the production of non-alcoholic fermented beverages in Africa and Mexico, as well as in the production of alcoholic beverages such as beer. In China, it is utilized in the production of alcoholic drinks and vinegar. Additionally, it can be preferred as a substitute for wheat in the production of gluten-free foods, including pasta, bread, biscuits, and oatmeal (Pineli et al., 2015; Chavez et al., 2018; Khoddami et al., 2023).

The sorghum species, specifically *Sorghum bicolor* (L.) Moench, stands out as the most widely cultivated type globally. This type, which achieves high yields, is a self-pollinating plant and belongs to the C4 type (Gomez-Martinez and Culham, 2000; Goyal et al., 2020). Sorghum is a highly drought-resistant species (Wagaw, 2019) and is cultivated in the arid and semi-arid regions of Asia, Africa, the Middle East, Australia, and North and Central America (Khoddami et al., 2023). It also possesses the ability to survive in cool temperatures (12-15 °C), endure short periods of waterlogging, and thrive in regions with high rainfall (Lim, 2012). The leading countries in sorghum cultivation are the United States, Ethiopia, Nigeria, Sudan, India, and Mexico, followed by Argentina, China, Brazil, and Niger (USDA-FAS 2021).

There are around 25 species associated with the Sorghum genus. The most agriculturally important species is *S. bicolor* (L.) Moench (Açıkgöz, 2021). Sorghum is a significant cereal crop with a high degree of genetic and phenotypic variability, both within *S. bicolor* and among its wild relatives (Mace et al., 2021). Sorghum varieties can vary in terms of the appearance quality and color of their grains, the presence or absence of the testa layer, the thickness and color of the pericarp, and additionally, the genes that control endosperm thickness and color (Rooney and Miller, 1982). Sorghum varieties have been classified based on various criteria (Shin, 1986). Some of these include taxonomy, such as leaves, flowers, panicles, seed size, pericarp, testa, and endosperm. Plants are classified into different sorghum types based on their responses to environmental conditions such as temperature, photoperiod, drought, and humidity. In terms of usage, sorghum varieties are categorized as sweet sorghum for biofuel, broomcorn and brush sorghum for brooms, and grain sorghum for human consumption and animal feed (USDA-FGIS, 2009).

Sorghums are annual plants with a strong root system. In some species, support roots can emerge from the aboveground nodes. With a fibrous root structure, sorghums demonstrate resilience to drought conditions, as roots can spread deep and wide. Stem thickness can range from 2-5 cm, and new shoots can emerge from the nodes at the lower part of the stem. Açıkgöz (2021) reported that the plant height is around 100 cm for grain production, while some hybrid varieties bred for forage production can reach up to 4-6 meters. The leaves are narrow with toothed edges, and the upper part of the leaf sheath is covered with a waxy layer. The inner glumes of sorghum flowers can be awnless or awned, and the inflorescence is in the form of a panicle. Sorghum seeds can vary in color, including white, yellow, red, and brown. In grain types, sorghum seeds are larger, while in forage types, they are smaller. Fribourg (1995) reported that sorghum varieties can grow in almost all types of soil, with the optimum pH being between 6.0-6.5. Additionally, it was mentioned that sorghum is highly tolerant to acidity.

1. SORGHUM SECONDARY METABOLITE CONTENT

Organic compounds produced by plants or microorganisms that are not directly involved in the growth, reproduction, and development of organisms are referred to as secondary metabolites. Secondary metabolites are as crucial to the vital functions of plants as primary metabolites, as they contribute to the plant's resistance to pests, diseases, and adverse environmental conditions, and exhibit allelopathic effects against some weeds. Humans utilize secondary metabolites in medications, flavorings, pigments, and perfumes (Ramakrishna and Ravishankar, 2011; Bakır, 2020; Tiring et al., 2021). Additionally, there are secondary metabolites in humans that possess pharmaceutical, nutraceutical, and toxicological effects (Wink, 2013; Kazlauskaite et al., 2023).

The structure and components of secondary metabolites can vary depending on the plant species. It has been reported that in the composition of *S. bicolor* grain, pericarp constitutes 3-6%, and endosperm constitutes 84-90% of the grain, with ferulic acid being the dominant phenolic acid (Boz, 2016). Sorghum grains contain flavonoids. These flavonoids include flavones (luteolin and apigenin), flavanones (naringenin), and flavonols (kaempferol and quercetin) (Przybylska-Balcerek et al., 2019).

There can be variations in tannin content among different sorghum varieties. While some grains may contain more than 90% tannins, in others, this ratio can drop to the 2% range. The reason for this decrease is the absence of a pigmented testa in sorghum grains (USDA-FGIS, 2009). Sorghum varieties with high tannin content are preferred by farmers due to their resilience to extreme weather conditions, resistance to birds and insects, and the prominence of high yield potential (Lubadde et al., 2019). However, tannins are an important nutritional constraint for grain consumption by animals or humans. It has been reported that tannins have an effect in reducing the digestibility of protein and starch and are effective in reducing weight gain in monogastric animals such as rabbits and chicken (Muriu et al., 2002; Liu et al., 2015). Some studies have confirmed the effect of tannins in reducing the digestibility of protein and starch in sorghums through in vitro tests (Barros et al., 2014; Dunn et al., 2015). In terms of potential health effects, it has been stated that the lipid extract in sorghum grains without tannins is effective in lowering cholesterol absorption, attributed to containing sterols and policosanols in the grain lipid fraction (Carr et al., 2005).

2. THE EFFECTS OF SECONDARY METABOLITES IN SORGHUM SPECIES ON HUMAN HEALTH

Secondary metabolites can be used by humans as antioxidants or as raw materials for medicine. It is known that the secondary metabolites contained in each plant are different. The secondary metabolites found in the sorghum plant (*S. bicolor* L. Moench) include tannins, alkaloids, saponins, terpenoids, flavonoids, polyphenols, and steroids (Setyorini and Antarlina, 2022).

Among the fundamental structural features of phenolic compounds are aromatic rings carrying one or more hydroxyl groups (Chirinos et al., 2009). Plant phenolic compounds can be classified as polyphenols or phenols depending on the number of phenol units in the molecule. Within plant phenols, there are lignins, simple phenols, lignans, coumarins, phenolic acids, condensable and hydrolysable tannins, and flavonoids (Soto-Vaca et al., 2012). Phenolic compounds are synthesized in plants partly in response to physiological and ecological stresses, including UV radiation, insect and pathogen attacks, and injury (Diaz Napal et al., 2010; Kennedy and Wightman, 2011). These phytochemicals function as antioxidants, contributing to the prevention of heart disease (Wijngaard et al., 2009; Dai and Mumper, 2010). Additionally, they can be used in the treatment of diseases such as diabetes (Scalbert et al., 2005; Thompson et al., 1984) and cancer (Sawadogo et al., 2012).

One of the significant secondary metabolites present in sorghum is ß-glucan. It is known that this component has positive effects, particularly in terms of prebiotics, in preventing diabetes and colon cancer (Niba and Hoffman, 2003). ß-glucan has been reported to be effective in anti-tumor and antimicrobial stimulation (Brown and Gordon, 2001), lowering blood glucose and cholesterol levels (Khan et al., 2021), and contributing to weight loss (Rehman et al., 2021).

Studies on the phytochemicals in sorghum, especially anthocyanins and other flavonoids, have reported various effects, including immunomodulatory (Chung et al., 2011), anti-inflammatory (Bralley et al., 2008; Shim et al., 2013), anticancer (Chen et al., 2011; Massey et al., 2014), antimicrobial (Mohamed et al., 2009; Svensson et al., 2010), anti-cardiovascular disease (Mellen et al., 2008), anti-lipidemic (Chung et al., 2011), anti-anemic (Oladiji et al., 2007), neuroprotective (Oboh et al., 2010), and anti-diabetic (Farrar et al., 2008; Hargrove et al., 2011) effects.

The nutrients in sorghum grains play a positive role in human health and nutrition, especially for those dealing with celiac disease, diabetes, and obesity (Zhang and Hamaker 2009; Birt et al., 2013; Pontieri et al., 2013; Lemilioglu-Austin, 2014; Benkadri et al., 2018; Pestorić et al., 2017; Shahzad et al., 2021). Generally, the phenolic compounds in sorghum are not commonly found in other cereal grains (Awika, 2011; Awika and Rooney, 2004). It has been stated that sorghum, through its secondary metabolite polyphenols, has a greater potential for suppressing the proliferation of cancer cells compared to other food sources (Awika 2017). In another study, Moraes et al. (2012) reported that monomeric flavonoids have varying levels of anti-inflammatory effects, which are effective in preventing and reducing cancer progression and development (Park et al., 2012; Xie et al., 2019).

It has been reported that the phenolics and other components in sorghum have important properties such as cancer prevention, cardiovascular health, and reducing chronic inflammation and oxidative stress (Yang et al., 2015). Additionally, it has been suggested that polymeric sorghum polyphenols, namely tannins, can be used as a natural ingredient to reduce the caloric impact of starch (Amoako and Awika, 2016).

3. CONCLUSION

Sorghum varieties are a highly potential food source in terms of secondary metabolites. Sorghum contains numerous secondary metabolites such as phenolic acids, alkaloids, tannins, flavonoids, polyphenols, terpenoids, saponins, steroids, phytosterols, anthocyanins, and policosanols. Many of these secondary metabolites present in sorghum are being evaluated for their impact on human health. Upon examination of these secondary metabolites in sorghum, it has been observed that they are beneficial for human health, effective in the treatment of various diseases, and contribute to reducing the impact of certain conditions. The secondary metabolites in sorghum have been found to play a role in reducing the development and occurrence of cancer, suppressing the proliferation of cancer cells, addressing conditions like celiac disease, diabetes, and obesity, lowering cholesterol levels, and preventing heart disease.

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ISBN: 978-625-367-599-8