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

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PREFACE

Medicinal and aromatic plants are used not only in the pharmaceutical industry, but also in cosmetics and food industries, plant protection products, and landscaping. In recent years, the medicinal benefits of these plants have gained an important place in the pharmaceutical industry with the increase in scientific studies. In addition, with the increasing interest in natural and organic products and the rise in environmental awareness, the use of medicinal and aromatic plants is increasing day by day. This book covers the different uses of medicinal and aromatic plants, their pharmacological properties, biological activities, and their use in modern medicine and folk medicine.

This book, which covers medicinal and aromatic plants from different aspects and was prepared with the participation of valuable researchers, consists of 13 chapters. We would like to thank all our authors who contributed to the preparation of this book titled 'MEDICINAL PLANTS: SECONDARY METABOLITIES, UTILIZATION, HUMAN HEALTH-II', and the employees of IKSAD Publishing House who contributed to the publication phase, and we hope that this book will be beneficial to the scientific community.

Sincerely

Assoc. Prof. Dr. Gülen ÖZYAZICI

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CHAPTER I

EFFECTS OF SALICYLIC ACID ON THE AMOUNT AND COMPOSITION OF ESSENTIAL OILS IN MEDICINAL AND AROMATIC PLANTS

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INTRODUCTION

Medicinal and aromatic plants have been of great importance as therapeutic, food and cosmetic products since the existence of humanity. This importance continues to increase today (Vartak et al., 2022). These plants, which are directly related to human nutrition and health, can only show the expected effects and provide the desired taste, smell and color with their quality (Chaachouay and Zidane, 2024).

The change of substances entering the living organism, from the moment they enter the cell to the formation of the final products, constitutes metabolism. Molecules that form the building blocks of all living things are called primary metabolites (carbohydrates, lipids, proteins, nucleic acids and enzymes) (Judge and Dodd, 2020). Other substances that are not directly related to living activities and are produced because of secondary metabolism only in certain organisms, species, species or tissues because of primary metabolism are defined as secondary metabolites (Twaij and Hasan, 2022). Secondary metabolites are compounds that are synthesized during the growth of plants and do not play an active role in development, photosynthesis and reproduction. However, these compounds play a critical role in the defense of plants against biotic and abiotic stress factors (Cohen and Kennedy, 2010; Twaij and Hasan, 2022).

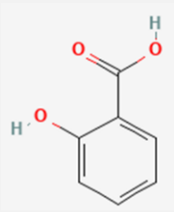
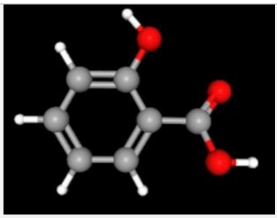
Medicinal and aromatic plants are important sources of secondary metabolites. Stress factors accelerate secondary metabolite synthesis (Cohen and Kennedy, 2010; Jenks, 2007). It has been stated that secondary metabolite synthesis can be controlled by creating similar effects during plant cultivation. For this purpose, external stimulant chemicals (acetic acid, ethanol, hydrogen peroxide, jasmonic acid, GA_3

etc.) can be used on plants (Baenas et al., 2014). One of these stimulant chemicals is salicylic acid (SA). SA is a growth regulator for plants and controls defense processes against biotic/abiotic stress (Cohen and Kennedy, 2010).

1. SALICYLIC ACID

It takes its name from the willow tree (*Salix alba* L.) from which it was first isolated. Salicylic acid (SA) is an endogenous growth regulator with a phenolic structure consisting of a ring connected to a hydroxyl and a carboxyl group, which plays a role in the regulation of physiological processes in the plant (He et al., 2005). Some information about SA is presented in Table 1.

Table 1. Some general information about SA[1]

Salicylic Acid	**o-hidroksibenzoik asit**
Molecular Formula	$C_7H_6O_3$ HOC6H4COOH
Molecular Weight	138.12 g/mol
Chemical Structure	 
Color	Colorless/white
Odor	Odorless
Form / Appearance	Crystalline powder
Melting point	157-159°C

[1]National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 338, Salicylic Acid. Retrieved September 12, 2024, from https://pubchem.ncbi.nlm.nih.gov/compound/Salicylic-Acid.

The developmental stages of studies on salicylic acid throughout the historical process are shown in Figure 1.

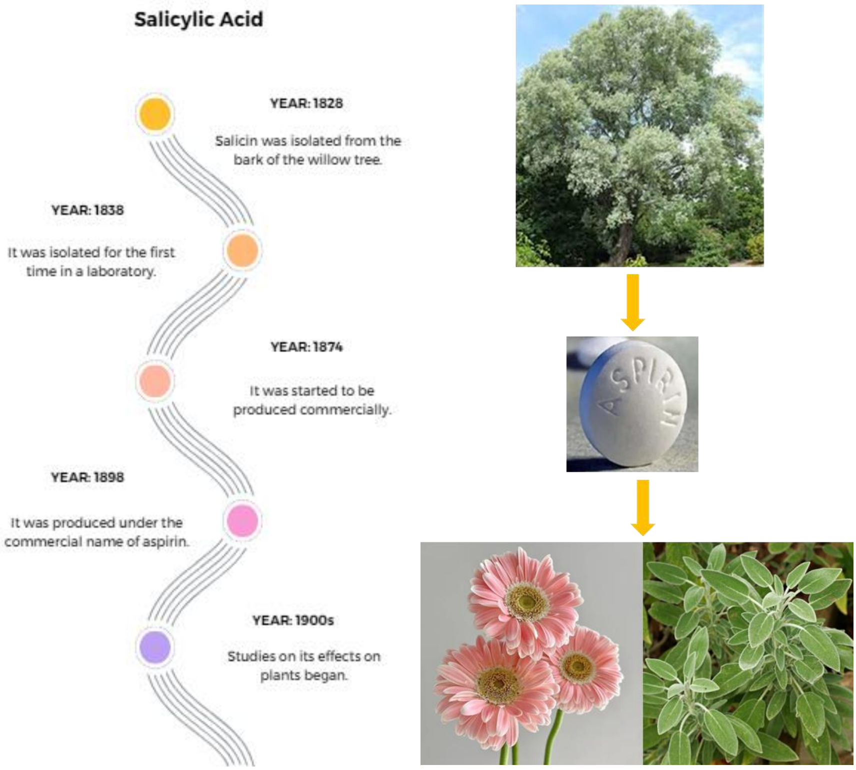


Figure 1. Salicylic acid studies from past to present

Benzoic acid derivatives, including salicylic acid, are formed by removing a C2 moiety from phenylpropanes (Widhalm and Dudareva, 2015). Aspirin (= Acetyl Salicylic Acid) is an analogue of SA. It hydrolyzes shortly after contact with water and turns into SA (López Fernández et al., 1990). For medical purposes, SA is widely used today against colds, pain, fever and heart disease and is probably the most widely used drug in the world. The name salicylic acid comes from the

Latin name of willow, Salix, since it was first isolated from the bark of the willow tree, where it accumulates in high quantities (Heldt and Piechulla, 2015).

SA is an important growth factor and a valuable phytohormone found in many plants (Li et al., 2022). Phytohormones act as endogenous signals at very low doses to regulate various physiological functions and can affect different parts of the plant after exogenous application (El Sabagh et al., 2022). Plants rapidly produce SA when exposed to biotic (disease and pest) and abiotic (heat, cold, light, drought, salinity, heavy metal toxicity, etc.) stress factors. SA plays an important role in the defense mechanisms of plants. When applied exogenously, it increases the plant's tolerance to heat, cold and salt stress (Song et al., 2023). SA prolongs the survival time in cut flowers and stimulates flowering in plants under adverse conditions. Also, it promotes early leaf senescence and promotes secondary metabolite formation in cell cultures or living plants (Martínez et al., 2004; Guo et al., 2021).

Exogenous application of SA affects growth and development depending on the plant species, developmental stage and SA concentration used. Low concentration promotes growth in some plant species. High SA concentrations cause serious growth retardation. When SA applied exogenously, it can inhibit germination or positively promote germination by increasing seed viability, depending on the application dose. SA also has a regulatory effect on photosynthesis. It has been observed that SA affects the structure of leaves, regulates stomatal closure, and affects the structural state of chloroplasts and both chlorophyll and carotenoid accumulation. On the other hand, it controls the activity of important enzymes that are effective in photosynthesis (Rivas-San Vicente and Plasencia, 2011; Torun et al., 2022).

SA contributes to the regulation of different oxidase pathways in plants (thermogenic/non-thermogenic). SA has positive effects on plant growth. It achieves this effect by "changing the hormone balance of plants, increasing photosynthetic activity, regulating transpiration and affecting stomatal conductance" (Lefevere et al., 2020).

2. ESSENTIAL OIL

Plants synthesize two types of oils: fixed and essential oils. Fixed oils are glycerides formed by the esterification of glycerol and fatty acids (Taşkor Önel and Yaman Akbay, 2022). Essential oils are also called etheric oils. Essential oils are products obtained from a natural raw material of plant origin by distillation (water, steam, water and steam) or mechanically (cold press) (Durczyńska and Żukowska, 2024).

Essential oils, common in aromatic plants, are a mixture of lipophilic and odorous substances (Zhang et al., 2024). Essential oils are usually colorless or very pale yellow. They have a density less than water and are liquid at room temperature, evaporating when left open and leaving no permanent stains. Some essential oils (e.g. cinnamon essential oil) are not liquid at room temperature. Essential oils are generally slightly soluble in water, very soluble in ethanol and most organic solvents and oils. They are lighter than water, except for clove and cinnamon essential oils. They do not saponify. They have a high refractive index. They are optically active. Pharmacologically, they exhibit broad biological activity (antimicrobial, antioxidant, antitumor, antiviral etc.) (Mugao et al., 2020; de Sousa et al., 2023; Zhou et al., 2023).

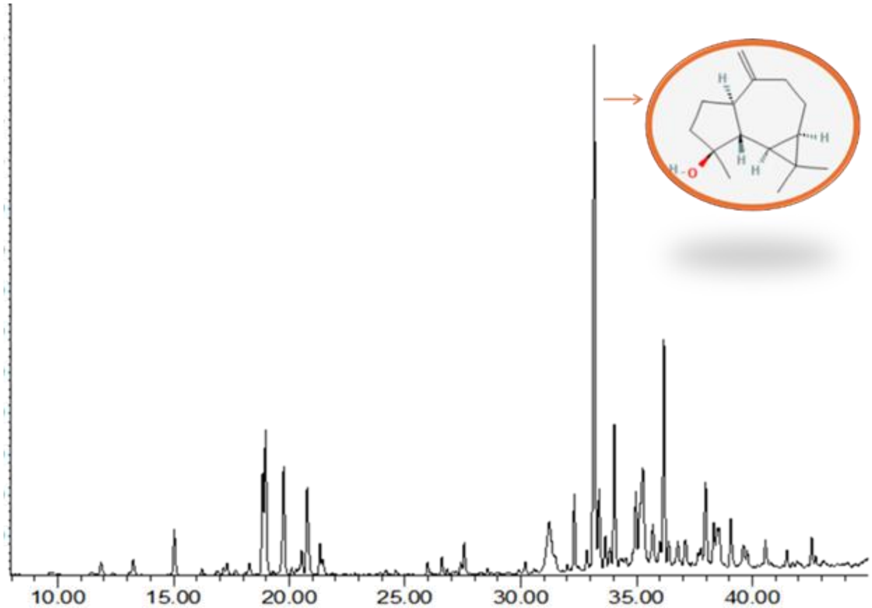


Figure 2. Chemical components of *Salvia cyanescens* BOIS. & BALANSA (endemic) herba essential oil in the GC/MS analysis result.
[42 components were detected in the essential oil. Spathulenol was recorded as the main component (~18%)].

Essential oils contain many components with different concentrations. The number of components usually varies between 20 and 60, but there are essential oils that contain fewer or more components. The concentration of some components/a component in essential oils may be higher than others. These are called main components. Other components are referred to as minor components. The main components are responsible for the biological activity of essential oils. However, minor components also create a synergistic effect by strengthening the biological activity of the main component/components (Figure 2) (Sarkic and Stappen, 2018; Mugao et al., 2020; Sharmeen et al., 2021; de Sousa et al., 2023).

Essential oils are generally found in certain amounts in glandular hairs, glandular cells, or secretory cells, depending on the family to which the plant belongs. Sometimes they are found in modified parenchyma cells, in glycoside form or together with gums and resins (Gostin and Blidar, 2024; Mugao, 2024). Essential oils can be found in every organ of the plant (Figure 3) (de Sousa et al., 2023).

Herbal drugs contain different amounts of essential oil (Mugao et al., 2020). Essential oils are generally composed of hydrocarbons and their oxygenated derivatives. These include alcohols, acids, esters, aldehydes, ketones, amines and sulfur compounds. The most common compounds in essential oils are mono-, sesqui- and diterpenes and their oxygenated derivatives, terpenoids (Sridhar et al., 2003; González-Mas et al., 2019).

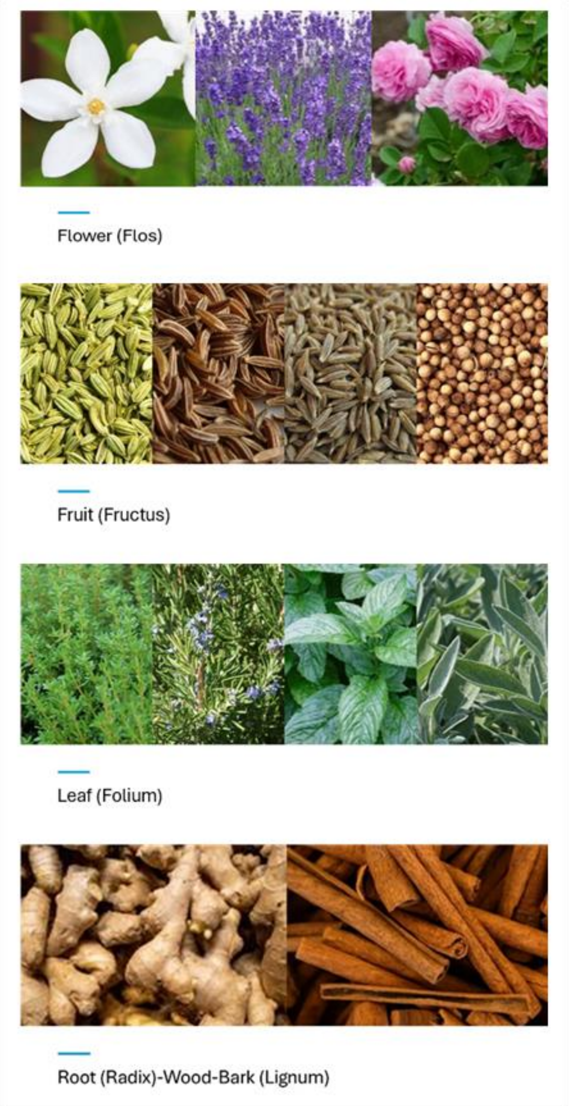


Figure 3. Plant parts containing essential oils [Flower (Flos)-Lavender, Rose, Jasmine; Fruit (Fructus)-Anise, Cumin, Coriander, Fennel; Leaf (Folium)-Thyme, Rosemary, Sage, Mint; Root (Radix)-Ginger; Wood-Bark (Lignum)-Cinnamon (From right to left in order)]

3. EFFECTS OF SALICYLIC ACID ON THE AMOUNT AND COMPOSITION OF ESSENTIAL OILS IN MEDICINAL AND AROMATIC PLANTS

There are many factors that affect the yield and composition of essential oil obtained from plants (Tahan et al., 2020; Katar et al., 2021; Mogao, 2024):

-Essential oil extraction method,

-Environmental conditions (temperature, soil plant nutrients etc.),

-Cultural practices (sowing/planting time, irrigation, fertilization, harvest time, harvest period, post-harvest processes etc.),

-Stress factors,

-Plant growth regulators etc.

Plants sensing environmental stress activate several defense mechanisms that can be artificially induced or enhanced by the application of certain chemicals (Raskin, 1995; Rajasekaran and Blake, 1999). Under stress conditions, SA has ameliorative effects on plant growth (nutrient uptake, maintenance of membrane stability, water level, stomatal regulation, inhibition of photosynthetic biosynthesis and ethylene biosynthesis). SA plays a role in plant responses to abiotic stress conditions (drought, etc.) and controls gene expression. Most genes regulated by SA are responsible for defense. SA can alter secondary metabolites and secondary metabolite synthesis pathways due to its effects on chlorophyll levels. This affects the composition of essential oils (Emamverdian et al., 2020; Elsisi et al., 2024).

SA affects various physiological and biochemical activities of plants. It has important effects on the regulation of both growth and productivity of plants. Exogenous application of SA can affect the synthesis of some proteins and enzymes in carbohydrate/energy metabolism in the plant. This also changes the synthesis of secondary metabolites. Exogenous application of SA has been observed to have a positive effect on secondary metabolite production in both cell cultures and living plants. It has been determined that the quantity and quality components of the essential oil obtained from plants change with SA application. The research findings including the effects of SA application on the amount of essential oil and essential oil composition in some medicinal and aromatic plants are summarized in Table 1.

SA acts as a plant growth regulator. SA applied to plant leaves causes an increase in plant growth, nutrient uptake or changes in leaf structure. This changes the amount of essential oil and chemical composition of the plant when applied from the leaf. The increase in the amount of essential oil varies according to the SA concentration. Increasing doses decrease the amount of essential oil after a certain level.

SA is considered as a signaling molecule involved in some signal transduction systems, enabling certain enzymes to up- or down-regulate proline and glycine betaine, which are defense compounds or compatible solutes, under stress conditions. Therefore, SA, as a natural plant hormone, can be applied in production systems, especially to increase the yield of essential oil. (Buker et al., 2016)

The stimulatory effects of SA on the essential oil composition can be attributed to the effects of salicylic acid on the improvement of nutrient uptake, cell elongation, cell division, cell differentiation, changes in hormonal status, photosynthesis, transpiration and stomatal conductance, which reflect various increases in the essential oil composition (Blokhina et al., 2003; El-Tayep, 2005; Shakirova, 2007; Abreu and Munne-Bosch, 2009). SA improved the level of cell metabolism, which is a prerequisite for the synthesis of auxin and/or cytokinin, which may lead to an increase in the essential oil composition (Metwally et al., 2003; Gharib, 2006). In addition, SA increased the number of oil-bearing glands and the enzyme activities of mono- and sesquiterpene biosynthesis, thus increasing the amount and composition of essential oil (Rowshan and Bahmanzadegan, 2013). SA application is a practical approach to increase the essential oil accumulation (Said-Al Ahl et al., 2016).

Table 1. Effects of SA application on the amount and composition of essential oil in some medicinal and aromatic plants

TAXON	APPLICATION	EFFECT	REFERENCES
Salvia macrosiphon Boiss.	-Full flowering stage -Control, 0 mgL^{-1}, 200 mgL^{-1}, and 400 mgL^{-1} spray SA application -Aerial parts were harvested at the flowering stage one week after SA application.	Essential oil yield increased from 0.23% (0 mgL^{-1}) to 0.48% (400 mgL^{-1}) Linalool amount increased δ-cadinene and sclareol amounts decreased.	Rowshan et al., 2010
Nepeta cataria L. *Nepeta cataria* var. *critriodora* Beck.	Spraying 0 and 200 mgL^{-1} SA	Increase in the amount of essential oil.	Said-Al Ahl et al., 2016
Achillea millefolium Boiss.	-Exogenous application of SA (control, 200 and 400 mgL^{-1}) at early flowering stage. Distilled water was used as control. -After one application at full flowering stage, aerial parts were harvested.	Change in essential oil composition	Rowshan and Bahmazzadegan, 2013
Mentha piperita L.	-Application of SA at different concentrations (0, 75, 150, 300, 450 mgL^{-1}) as foliar spray three times during plant growth -First foliar application: two	The amounts of essential oil in 0, 75, 150, 300, and 450 mgL^{-1} SA applications were 2.32%, 2.33%, 2.55%, 2.44%, and 2.21%, respectively	

	months after rhizome placement -Second application: 10 days after flowering -Third application: 10 days after the beginning of flowering -Control plants (0 mgL-1 salicylic acid) at the same times ethanol:water 1:1000, v/v		
Orange peels and leaves	Spray application	SA:0, 20, 40 mgL^{-1}; Control: Distilled Water Essential Oil Change According to Doses: In young leaves, respectively: 0.2-0.3%, 0.3-0.4%, 0.5-0.6% In peels, respectively: 0.2-0.3%, 0.5%, 0.8-0.9%	Klalid and Ahmed, 2019
Satureja hortensis L.	Application of 0, 5, 10, 20 mgL^{-1} SA as a spray on leaves	Increase in carvacrol, ɣ-terpinene and monoterpene hydrocarbons at 5 mgL^{-1} SA application	Pirbalouti et al., 2016
Mentha x piperita L.	40, 80, 160 and 320 mgL^{-1} as foliar spray	Increase in the amount of menthone, neomenthol, piperitone and ɣ-terpinene in 320 mgL^{-1} SA application	Motiee and Abdoli, 2021

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CHAPTER II

AN OVERVIEW OF THE HEALTH BENEFITS OF GLOBE ARTICHOKE (*Cynara cardunculus* var. *scolymus*)

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INTRODUCTION

The '*Cynara*' genus, to which the artichoke belongs *Asteraceae* family, is endemic to the Mediterranean region, Southern Europe, and Northwest Africa. In the ice age, it emerged from the southern Mediterranean region and toward the ends of the ice age it spread to the Sahara. It also expanded to the eastern and western Mediterranean. Wild artichoke, or "cardoon," is cultivated widely around the world today (Ciancolini, 2012).

The *Cynara* genus name is said to have come from the Greek term *skolymos*, which means thistle or thorny plant, and the Latin words *cinis* and/or *cineris*, which refer to the practice of fertilizing plants with ashes (Lattanzio et al., 2009). The Arabic word ‘al-harshúf’ is the origin of the names carciofo, alcachofa, and alcachofra for globe artichokes in various countries including Italy, Spain, and Portugal. The plant's spread throughout the Mediterranean region is believed to have been facilitated by Arabs. The Latin term *articoculum* which combines the words *artus*, which means prickly, and *cocolum*, which means sphere - remains at the root of the name of plant for England, France, and Germany.

Several researchers have noted that there are two distinct groups within the genus *Cynara*. While *C. cardunculus*, which includes both wild and cultivated artichokes, makes up the first group, the second group is more diverse, comprising seven wild species with broad, spiny leaves and heads (Pignone and Sonnante, 2009; Ciancolini, 2012). According to Pignone and Sonnante (2009), wild artichokes are still known to exist today. As previously established by Pignone and Sonnante (2009), the primary cause of the genetic variation between the species is the wild artichokes. Wild artichokes exist in three different botanical forms (Migliori, 1995; Ekbiç, 2005; de Falco et al., 2015):

- Cultivated wild artichoke - *Cynara cardunculus* L. var. *altilis* D.C.
- Cultured artichoke, also known as 'globe artichoke' - *Cynara cardunculus* L. *Cynara scolymus* L.
- *Cynara cardunculus* L. var. *silvestris* Lam., defined as wild artichoke and known as 'cardoon'.

The herbaceous artichoke plant may grow up to 1.80 meters in height. The globe-shaped flower head has bracts on the outside that are green and violet. The bristle-based "choke" is positioned above the receptacle, which is positioned in the bottom section of the globe artichoke head. In the middle of the head are many blue-purple blooms. This plant is frequently used for medicinal purposes and is a staple of the Mediterranean cuisine (Pereira et al., 2015; Di Napoli et al., 2023).

Globe artichokes are a vegetable that may be eaten frozen, tinned, or fresh. The consumable parts of the plant are the inner bract leaves of the immatured flowers (heads, buds, or capitula) and the flower receptacle (heart); the bract leaves on the outside of the head, leaves, and stem are industrial secondary products (Figure 1). According to Ruiz-Aceituno et al. (2016), these are the sections of the artichoke plant that are not edible. According to research, 100 g of fresh artichokes, which are high in vitamins and minerals, contain around 10 g of carbs, 3 g of protein, and 0.3 g of fat. They also include 88–90% water. Globe artichokes are a highly useful vegetable in terms of health (Vural et al., 2000; Ekbiç, 2005).

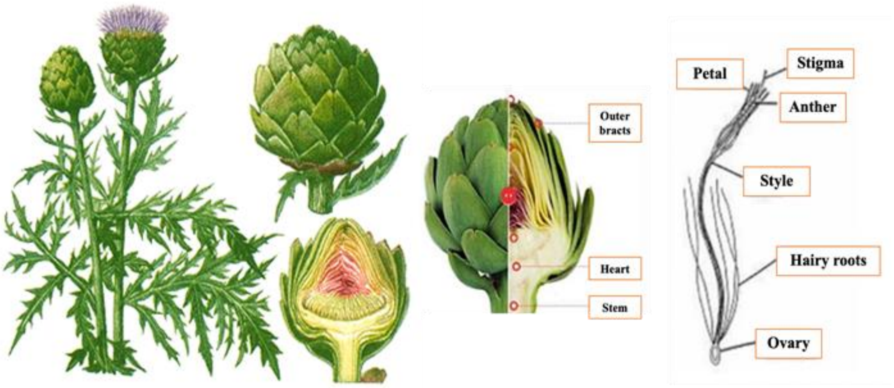


Figure 1. Structure of the globe artichoke plant (adapted from Ozsan, 2019)

1. NUTRITIONAL CHARACTERISTICS OF ARTICHOKES

The nutrients in artichokes' various botanical parts—the head, bracts, leaves, and stem—vary greatly (Al-Subhi, 2020; Al Amrani and Aneed, 2023). This variance is also caused by ecological (Allahdadi et al., 2017), harvest (Raccuia and Melilli, 2007; Lombardo et al., 2010), regional (Sękara et al., 2015), and genetic (Pandino et al., 2011a) variables. Petropoulos et al. (2018) state that artichokes have 79.73 kcal per 100 g edible amount and are regarded as a low-calorie meal because of their high level of moisture (around 80%) (Claus et al., 2015; Alicandri et al., 2023)

Artichoke heads contain 24.27% DW of protein. The macronutrient's content varies in various parts of the artichoke known as by-products; however, it is less in leaves (8.74%) (Magied et al., 2016) along with bracts (10.35%) (Claus et al., 2015). Essential amino acids make up around 41.04% of all amino acids, with proline and phenylalanine being the most prevalent aromatic amino acids, followed by leucine and valine, which are branched amino acids (El-Hadidy et al., 2022). However, compared to other vegetables like carrots, tomatoes, cauliflower, maize, or beans, artichokes are a greater provider of essential amino acids and can meet all of the needs for all amino acids (Hussein et al., 1999).

Artichokes have a 2–4% DW fat content, with the leaves having a greater fat content than the edible flower (Claus et al., 2015). Furthermore, artichokes have a fatty acid composition that is high in polyunsaturated fatty acids (PUFAs), which account for nearly half of all fatty acids (44.5%). The most common unsaturated fatty acid is linoleic acid, which has 55.20 mg per 100 g edible quantity. α-linolenic acid (20.40 mg/100 g) and palmitic acid (34.80 mg/100 g) come next (Dosi et al., 2013). Lastly, it was discovered that the main category of lipophilic substances present in cultivated artichoke and cardoon leaves were triterpenes and sesquiterpenes (Sharma et al., 2022). Up to 80% of artichokes' bitter flavor can be attributed to sesquiterpenes (Elsebai et al., 2016), of which cyanoropicrin is the most prevalent (Eljounaidi et al., 2014). According to reports, these bioactive substances have anti-inflammatory and anti-hyperlipidemic properties (de Falco et al., 2015).

An excellent supply of nutrients that organisms need is artichokes and their byproducts (Rocchetti et al., 2020). Globe artichokes constitute a great resource of potassium (K) and mostly iron (Fe) and zinc (Zn) comparing to the mineral composition of various vegetables that are discussed in the published works. Depending on the botanical section of artichoke, the concentration of macro- and microelements varies (Eman et al., 2018), although in general, all portions of artichokes may meet the mineral needs. Vitamins A, B, C, E, and K are abundant in artichoke heads. Specifically, artichokes are strong in vitamin C, with levels comparable to those found in blueberries, broccoli, and bananas. By promoting several naturally occurring and adaptive immune system cellular processes, this substance aids in immunological protection. Furthermore, vitamin C shields the body from oxidative stress caused by the environment and supports the function of the epithelial barrier against infections (Ahmad El-Sohaimy, 2013).

Artichokes' fiber content varies by plant part, between 31.47 and 85.28 g/100 g DW, with the floral stem having the highest fiber content. In terms of soluble dietary fiber, artichokes are high in pectins (20 g/100 g) (Zayed and Farag, 2020), the most prevalent of which is galacturonic acid. On the other hand, a significant amount of soluble fiber in artichokes is inulin (Christaki et al., 2012). A fluctuating amount of fructose units make up the structure of inulin, a fructan-type plant polysaccharide (Wan et al., 2020). All parts of the artichoke contain this chemical, however the stems have a higher concentration (25 g/100 g DW) (Fissore et al., 2014). Inulin is regarded as a prebiotic since it has been demonstrated to enhance intestinal flora and promote the synthesis of short-chain fatty acids (SCFA) (Fissore et al., 2015).

People should eat grains and fresh fruits and vegetables on a regular basis to maintain good health. There is no denying the importance of fresh fruits, vegetables, grains, and olive oil in a Mediterranean diet. Mediterranean diets are responsible for the high consumption of micronutrients (polyphenols, fibers, etc.), vitamins and minerals among its population (Pandino et al., 2011b). In this regard, artichokes are a valuable and commercially significant vegetable that may be consumed in a number of ways, including raw, boiled, or fried. They also have several health benefits. Because of their high biopharmaceutical content, which also adds to their health benefits, artichokes have apparently been utilized for food and medicine from ancient times (Ciancolini et al., 2013).

Nutraceuticals, also known as functional foods, are a relatively new word that has gained popularity in recent decades to describe a particular class of foods or "nutrients" with bioactive phytoconstituents that may have potential health advantages or “pharmaceutical applications”.

The artichoke is a prominent nutraceutical that is commonly incorporated into Mediterranean diets (Lombardo et al., 2015). Artichokes are rich in bioactive compounds. Polyphenols, including flavonoids and phenolic compounds, are abundant in the plant's tissues, derivatives of hydroxycinnamic acid, and lignans, which have various medicinal uses (Abu-Reidah et al., 2013; Dabbou et al., 2016; Blanco et al., 2018; Jiménez-Moreno et al., 2019). Hydroxycinnamic acids, which are generated from caffeic acid, are the most prevalent phenolic chemicals found in artichokes. The majority of the caffeic acid is converted to quinic acid to create caffeoylquinic derivatives. The most significant ones are cynarin, 1,5-*O*-dicaffeoylquinic acid, 5-*O*-caffeoylquinic acid, and 3-*O*-caffeoylquinic acid (Lattanzio et al., 2009). Despite the fact that the artichokes head contains the majority of these caffeic acid derivatives (Lombardo et al., 2010), the leaves and stems have been discovered to have larger concentrations of 5-*O*-caffeoylquinic acid (neochlorogenic acid) and 1,5-*O* dicaffeoylquinic acid (Pandino et al., 2013). The second most common type of naturally existing polyphenols in artichokes are flavonoids, especially flavones. Apigenin, luteolin, and its corresponding glycosides and rutosides are the most prevalent (Zhu et al., 2004). Artichokes lack flavonoids in the flower stalk and have them mostly in the leaves and head (Romani et al., 2006). These substances can shield cells from oxidative damage and have an anti-inflammatory impact (Ben Salem et al., 2017).

Anthocyanins, such as peonidin, delphinidin, and cyanidin, together with its glycosides of cyanidin, are other significant flavonoids found in artichokes (Schütz et al., 2004). In the cardiovascular system, these substances have been demonstrated to have a pro-inflammatory action (Xia et al., 2014). Additionally, these pigments are responsible for the green to violet hue of globe artichoke’s capitula (Lattanzio et al., 2009).

Globe artichokes can be categorized like a functional food (Ricceri and Barbagallo, 2016). In recent years, in response to people's increasing interest in functional foods, the artichoke plant has also taken its share, and extracts and capsules obtained from artichokes have begun to attract a lot of attention. In addition to being vegetable, decorative plant, and significant economic participant, globe artichokes are also excellent sources of a variety of bioactive substances, such as dietary fibers, polyphenols, flavonoids, coumarins, and terpenoids. Besides each class has a very diverse chemical profile (Pandino et al. 2011b).

2. HEALTH BENEFITS OF ARTICHOKES

There is evidence that the edible globe artichoke blossom may be beneficial to health. Artichoke, which has been known to be important for human health since Roman times, has some strong effects such as hepatoprotective, anticarcinogenic, antioxidative, antibacterial, and anticholesterol (Figure 2) (Schütz et al., 2004; Ciancolini et al., 2013; Ruiz-Aceituno et al., 2016; Lattanzio et al., 2019).

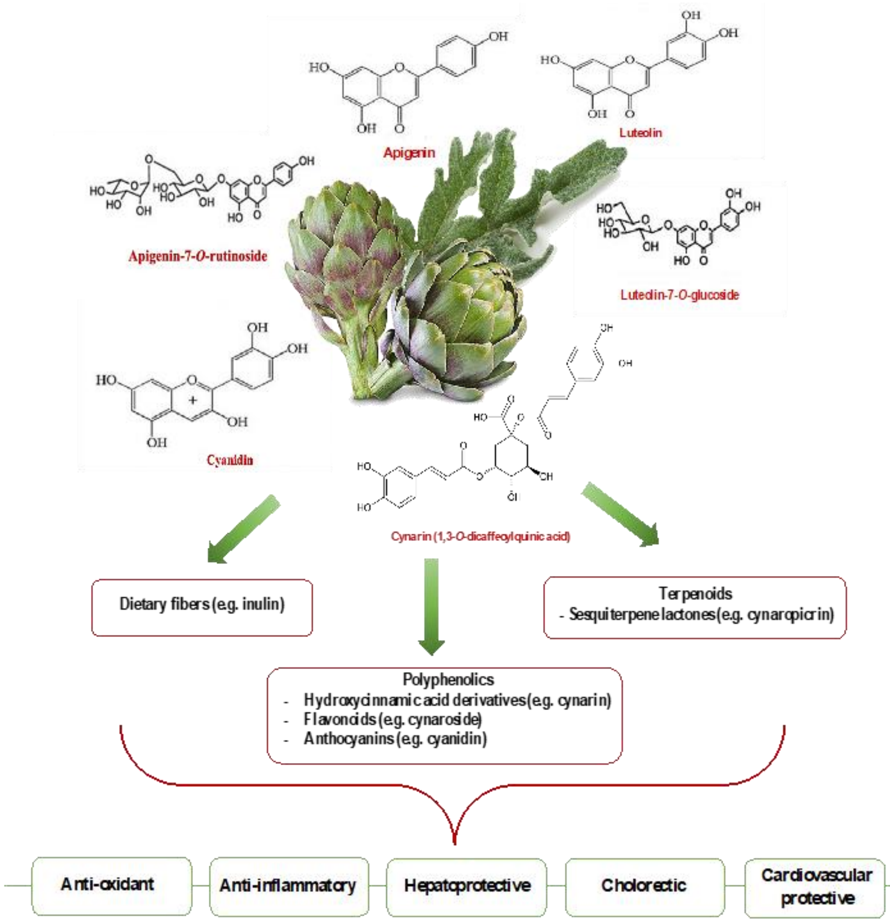


Figure 2. Potential bioactivities of globe artichoke regarding pharmacological mechanisms (adapted from Zayed et al., 2020)

Numerous bioactive substances, including vitamin C, derivatives of caffeic acid, apigenin, luteolin, and different anthocyanins, are present in *C. scolymus* L., as previously pointed out. These substances not only carry out vital tasks for the plant but, if consumed, can also protect against oxidative damage and the production of reactive oxygen species

(ROS) (Feiden et al., 2023). Compared to other plants like *Asparagus officinalis*, *Brassica oleracea*, *Cucumis sativus*, *Raphanus sativus*, *Brassica rapa* subsp. *rapa*, or *Beta vulgaris*, artichokes have greater ABTS and FRAP values due to their phenolic components (Tiveron et al., 2012). The heads and leaves are the primary sources of this potent antioxidant (Rejeb et al., 2020), but the remaining by-products of globe artichoke are a superior resource of phenolics compared to several more nourishments.

Many studies have shown that using various sections of artichokes can have a hepatoprotective effect against non-alcoholic fatty liver disease (NAFLD) (Moradi et al., 2021; Amini et al., 2022; Kamel and Farag, 2022). In the developing world, a higher risk of developing cirrhosis, liver cancer, and cardiovascular disorders is linked to non-alcoholic fatty liver disease (NAFLD), the most common reason of liver disorder, which affects 25% of adults worldwide (Younossi et al., 2018). Artichoke, which helps protect and renew the liver and encourages it to function (Pandino et al., 2011b), is therefore known as liver-friendly. Accordingly, it also reduces the risk of contracting hepatitis diseases. In addition, artichoke helps reduce cholesterol biosynthesis due to the luteolin substance it contains (Ruiz-Aceituno et al., 2016), protecting the heart by lowering bad cholesterol and increasing good cholesterol. Other positive health-related functions of the artichoke are preventing arteriosclerosis by contributing to the cleansing of the blood, ensuring the proper functioning of the kidneys, fighting against rheumatism and diabetes, as well as having positive effects on the digestive system and making positive contributions to the cleansing of the stomach and intestines.

Cynarin, one of the primary bioactive substances present in artichoke leaves, was discovered by Panizzi and his research team in 1954 (Lattanzio et al., 2019). It was at this time that the significant bioactive components of artichokes were first identified. This marked the beginning of the discovery of the important bioactive components of artichokes. Figure 3 shows the compounds that were discovered and classified into each biocompound class; Figures 4 and 5 provide some of the compounds' structures.

Figure 3. Globe artichoke biocompound groups and the main chemicals identified in each class

Biocompound classes		Chemical Compositions	References
Polyphenolics	**Hydroxycinnamic acid derivatives**	• Chlorogenic acid • Mono-caffeoylquinic acids ○ 1-*O*-caffeoylquinic acid ○ Cynarin (1,3-*O*-dicaffeoylquinic acid), ○ Chlorogenic acid (3-*O*-caffeoylquinic acid; 5-*O*-caffeoylquinic acid), ○ Cryptochlorogenic acid (4-*O*-caffeoylquinic acid), ○ Neochlorogenic acid (5-*O*-caffeoylquinic acid), • Di-caffeoylquinic acids ○ 1,4-*O*-dicafeoylquinic acid, ○ 1,5-*O*-dicafeoylquinic acid, ○ 3,4-*O*-dicaffeoylquinic acid, ○ 3,5-*O*-dicaffeoylquinic acid • Caffeic acid, • Ferulic acid	Wang et al. (2003), Zhu et al. (2004) Abu-Reidah et al. (2013)
	Flavonoids	• Flavones ○ Apigenin ○ Apigenin 7-*O*-glucoside ○ Apigenin 7-*O*-glucuronide ○ Apigenin 7-*O*-rutinoside or isorhoifolin ○ Luteolin ○ Luteolin 7-*O*-glucoside or cynaroside ○ Luteolin 7-*O*-glucuronide ○ Luteolin 7-*O*-rutinoside ○ Scolymoside • Flavanones ○ Naringenin ○ Narirutin (Naringenin 7-*O*-rutinoside) ○ Hesperidin	

Figure 3. continued

	Anthocyanins	• Cyanidin • Cyanidin 3-6″-malonyl glucoside, • Cyanidin 3,5-diglucoside cyanin, • Cyanidin 3-*O*-glucoside, • Cyanidin 3,5-malonyldiglucoside, and • Cyanidin 3-3″-malonyl glucoside • Peonidine • Delphinidin	Schutz et al. (2006)
Fibers or polysaccharides		• Pectin • Inulin	Fissore et al. (2015)
Terpenoids	**Monoterpenes**	• Myrtenal, • Isosylvestrene • Fenchone	Nassar et al. (2013), Dabbou et al. (2017)
	Sesquiterpenes	• β-selinene, • β-caryophyllene, and • α-cedrene	MacLeod et al. (1982), Dabbou et al. (2017), Santos et al. (2018)
	Sesquiterpene lactones	• Cynaropicrin, • Grosheimin, • Cynarinins A and B, • Cynarascoloside A-C, • Aguerin B, • Dehydrocynaropicrin, • Aguerin A • Cynartriol	Shimizu et al. (1988), Shimoda et al. (2003), Raccuia et al. (2011), Dabbou et al. (2017), Ramos et al. (2019)
	Triterpenes	• Cynarasaponins, • Lupeol • Taraxasteryl acetate	Krizkova et al. (2004), Nassar et al. (2013)

Figure 4. The molecular composition of some of the phenolic components present in globe artichokes (adapted from Farrag et al. 2023)

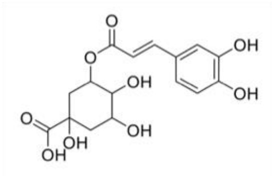
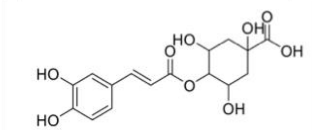
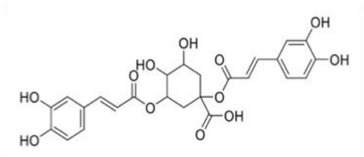
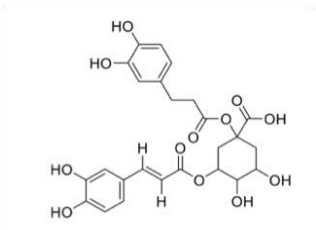
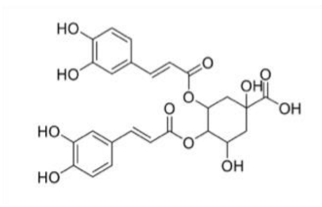
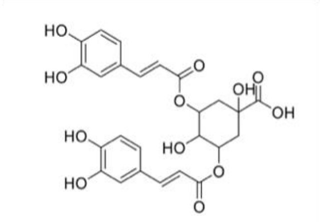
Phenolic compounds	Structure	Source	References
Chlorogenic acid		Flower heads, bracts, stem and roots	El Sayed et al., 2018; Farag et al., 2013; Khedr et al., 2022
4-*O*-caffeoylquinic acid		Bracts and floral stem	Farag et al., 2013; Mejri et al., 2020
1,3-*O*-dicaffeoylquinic acid (cynarin)		Flower heads, bracts, stem and roots	Farag et al., 2013; Khedr et al., 2022
1,5-*O*-dicaffeoylquinic acid		Flower heads and leaves	Shimoda et al., 2003; Farag et al., 2013
3,4-*O*-dicaffeoylquinic acid		Bracts, flower heads and floral stems	Shen et al., 2010; Mejri et al., 2020
3,5-*O*-dicaffeoylquinic acid		Bracts and stem	Zhu et al., 2004; Farag et al., 2013

Figure 4. continued

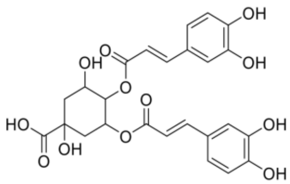
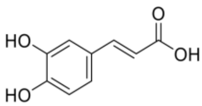
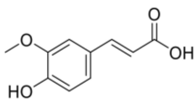
Phenolic compounds	Structure	Source	References
4,5-*O*-dicaffeoylquinic acid		Bracts and stem	Zhu et al., 2004
Caffeic acid		Flower heads, bracts and floral stems	Lattanzio et al., 1987; El Sayed et al., 2018;
Ferulic acid		Flower heads, bracts and floral stems	Lattanzio et al., 1987

Figure 5. Some flavonoids present in globe artichoke and their chemical structures (adapted from Farrag et al., 2023)

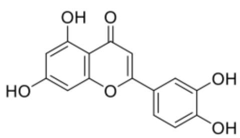
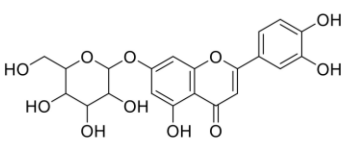
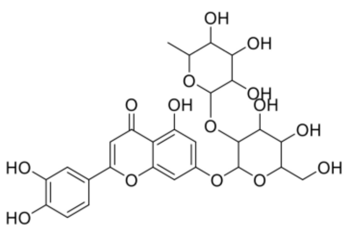
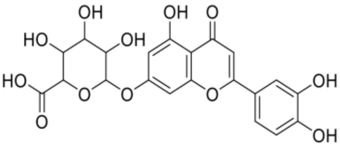
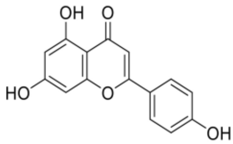
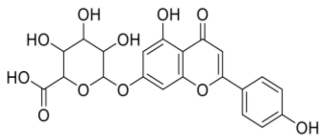
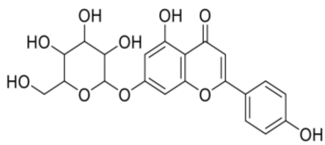
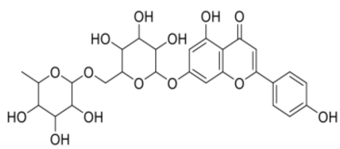
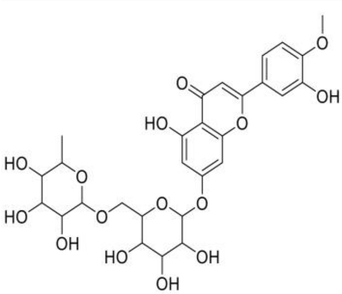
Flavonoids	Structure	Source	References
Luteolin		Flower heads, bracts, stem and roots	Schütz et al., 2006; El Sayed et al., 2018
Luteolin 7-*O*-glycoside (cynaroside)		Flower heads, bracts, stem and roots	Schütz et al., 2006; Farag et al., 2013
Luteolin 7-*O*-rutinoside (scolymoside)		Flower heads, bracts, stem and roots	Schütz et al., 2006; Farag et al., 2013; El Sayed et al., 2018

Figure 5. continued

Flavonoids	Structure	Source	References
Luteolin 7-*O*-glucuronide		Bracts, flower heads and floral stem	Romani et al., 2006
Apigenin		Flower heads, bracts, stem and roots	Schütz et al., 2006; Farag et al., 2013; El Sayed et al., 2018
Apigenin 7-*O*-glucuronide		Bracts and floral stem	Romani et al., 2006
Apigenin 7-*O*-glucoside		Flower heads, bracts, floral stem and roots	Hammouda et al., 1993
Apigenin 7-*O*-rutinoside		Bracts	Zhu et al., 2004; Abdel-Moneim et al., 2021
Hesperidin		Bracts	Hinou et al., 1989; Palermo et al., 2013

Twenty-two major compounds were identified through the qualitative detection of phenolics in the heads utilizing HPLC, MS, and DAD.ESI/MS; eleven of these were caffeoylquinic acids, and eight of these were flavonoids. The predominant compound in the flower heads is 1,5-di-*O*-caffeoylquinic acid, which is also present in pomace in good proportion. However, because to isomerization activities during the extraction process, 1,3-di-*O*-caffeoylquinic acid (cynarin) was the primary component in the juice (Al Amrani and Aneed, 2023).

Cynarin, which the leaves contain in large amounts, functions similarly to silymarin, which is present in *Silybum marianum* and protects the liver and promotes cell regeneration, is one of the most significant substances in artichokes that has therapeutic benefits (Aksu and Altinterim, 2013). This substance is frequently recognized as having therapeutic effects (Lattanzio et al., 2009).

Several research efforts have validated the function of artichokes in augmenting bile secretion and diminishing LDL and cholesterol, along with their association with the avoidance of heart disease and their anti-cancer properties (Lattanzio et al., 2009.; Bekheet and Sota, 2019; Zayed et al., 2020; Al Amrani and Aneed, 2023). Due to its role in increasing bile secretion, artichokes are also important for the management of intestinal issues, especially indigestion. The high-level phenolic compound concentration in artichoke leaves is responsible for many of its health benefits; the head and stems are the sections of the plant that are most frequently used for alleviating digestive problems. These portions have a high fiber content, especially inulin and pectins, which contribute to their anti-inflammatory and prebiotic qualities. The artichoke leaves have long been valued in traditional medicine for its protective qualities against hepatobiliary disorders and for its ability to help in digestion (Lattanzio et al., 2009; Lombardo et al., 2010). It also possesses hypolipidaemic and hypoglycemic impacts (Colantuono et al., 2018). The antibacterial and anti-HIV properties of artichoke (Dias et al., 2018; Lattanzio et al., 2009) were documented, along with its anti-inflammatory, antioxidant, anti-genotoxic, and anti-obesity properties (Kollia, 2017; Colantuono et al., 2018). On the other hand, among the most difficult issues facing industrialized nations with aging populations are conditions like Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal lobar dementia (Ransohoff, 2016). Compounds in artichokes have been demonstrated to have an important impact on lowering neuroinflammation (Figure 6).

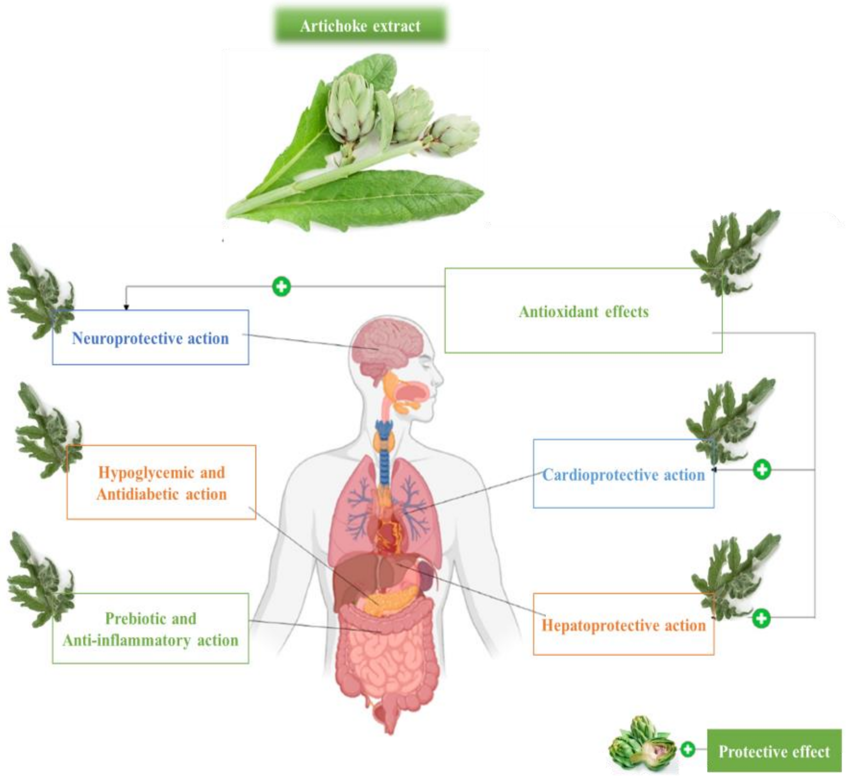


Figure 6. Beneficial impacts of *Cynara scolymus* L. on health (adapted from Ayuso et al., 2024)

An essential number of secondary compounds are polyphenols, which are involved in growth and development and function as a buffer against environmental stressors (Pandino et al., 2011b). Due to the phytochemicals, they contain, many edible plants have some health-promoting qualities; as a result, these plants are referred to as functional foods (Segasothy and Phillips, 1999). The major source of these important bioactive components, artichokes, substantially adds to their reputation as a particularly potent functional food.

3. CONCLUSIONS

Research until today, given the numerous health benefits of globe artichoke, it may be possible to find new, successful pharmacological findings that could serve as independently or additionally medicinal treatments. The plant's positive benefits on the liver, lipid profile, and antioxidant activity are the most often reported ones. Prebiotic and probiotic, antidiabetic, renoprotective, anticancer, antimetabolic, and anti-obesity actions are among the other health advantages, along with enhanced gastrointestinal and cardiovascular health. Although its cardioprotective and anti-hyperlipidemic properties have been thoroughly examined, the exact mechanism of action of *Cynara* natural compounds and how they collaborate with bodily enzymes to produce these effects are still not fully understood. It is believed that further research should be conducted regarding the molecular processes behind this plant's health-promoting characteristics as well as it should be considered to maximize the benefits of these bioactives and further evaluate their long-term safety and use.

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CHAPTER III

CHEMICAL CONSTITUENTS AND MEDICINAL BENEFITS OF *Coronilla* sp.

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INTRODUCTION

Among plant families, Fabaceae (Leguminosae) have a special importance the fact that they meet the basic food needs of humans as well as due to being a source of roughage in animal production and their versatile uses. Fabaceae is also known as the second-largest family of medicinal plants, and many of them are used as traditional therapeutic drugs in various parts of the world such as China, Japan, Iran, and India (Jamshidzadeh et al., 2018). In this sense, many species of the Fabaceae family have important secondary metabolites, which has led them to be considered as main components of pharmaceutical products.

The Fabaceae family consists of approximately 770 genera and over 19.500 species recorded in almost all of biomes on Earth (Lewis et al., 2005, 2013; Christenhusz and Byng, 2016). One of the important members of this family is the *Coronilla* L. genus. The species in this genus have very important agricultural characteristics such as being resistant to grazing due to the formation of rhizomes, having high biological nitrogen fixation capacity, being a high-quality, nutritious and productive forage plant, and being able to be used as green manure, ornamental and turfgrass plants (Zheng et al., 2016; Ma et al., 2024a). For all that, interest in *Coronilla* species as medicinal plants has increased due to the presence of pharmacologically active secondary metabolites in their content. In this sense, in recent years, phytochemical studies have focused on the chemical characterization of plant extracts and the determination of their biological activities. This review provides an examination of the chemical constituents and medicinal benefits of *Coronilla* species.

1. TAXONOMY AND DISTRIBUTION

Coronilla is a perennial forage plant which belongs to the family of Fabaceae. The plant also has significant medicinal value due to the secondary metabolites it contains. There are about 20 species in the *Coronilla* genus (Sokoloff, 2003; Açıkgöz, 2021). The taxonomic classification of this genus is given below:

Kingdom	**:** Plantae
Subkingdom	**:** Tracheobionta
Division	**:** Magnoliophyta
Class	**:** Magnoliopsida
Subclass	**:** Rosidae
Order	**:** Fabales
Family	**:** Fabaceae
Genus	**:** *Coronilla* L.

Coronilla sp. is a plant native to the Mediterranean region, Asia, Europe and North Africa (Al-Snafi, 2016). Many species of the genus *Coronilla* are found in the natural flora of Europe, Greece, Cyprus, Syria, Crimea, the Caucasus, Turkmenistan, North Africa, Tunisia, Iran, Iraq, Georgia, Armenia, Southern and Central Russia, Italy, the Balkans, Crete, Lebanon and Türkiye (Al-Snafi, 2016; Anonymous, 2024).

In Türkiye, *Coronilla glauca* L. is distributed in Southwestern Anatolia; *C. emerus* L. in the Aegean and Mediterranean regions; *C. scorpioides* (L.) Koch in the Marmara, Black Sea, Central Anatolia, Aegean and Mediterranean regions; *C. coronata* L. in Eastern Black Sea, Southern and Central Anatolia; *C. orientalis* Miller in the Black Sea, Central and Eastern Anatolia; *C. parviflora* Willd. in the Aegean and Mediterranean regions; *C. grandiflora* Boiss. in Mediterranean-Southern

Anatolia (endemic for Türkiye), *C. varia* L. subsp. *varia* L. is distributed throughout Türkiye and *C. varia* L. subsp. *libanotica* Bornm. in Southern Anatolia. The geographical distribution of 11 taxa of the *Coronilla* genus throughout Türkiye is given in Figure 1 (Anonymous, 2024).

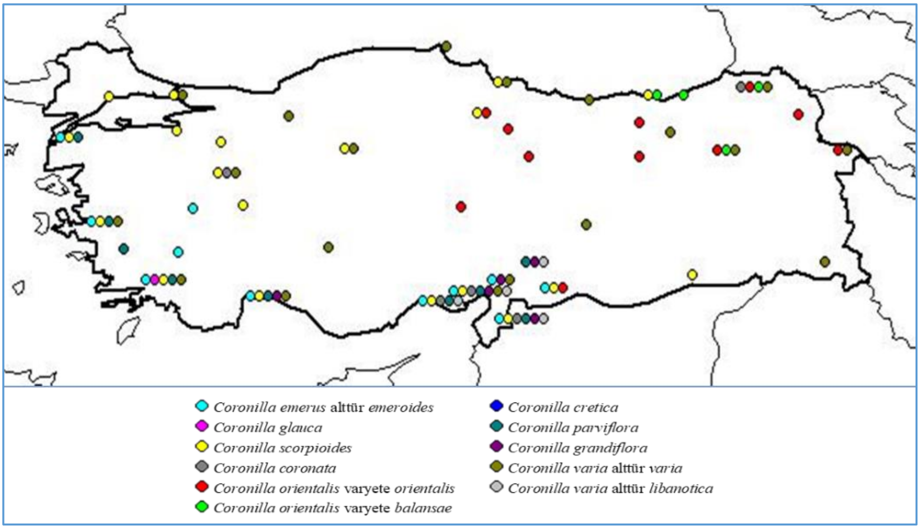

Figure 1. Geographic distribution of *Coronilla* species in Türkiye

2. CHEMICAL CONSTITUENTS OF *Coronilla* sp.

Many species in the *Coronilla* genus have a great importance as forage plants and superior properties in terms of chemical composition. For instance, *C. varia* is characterized by high biomass yield (Dronova et al., 2009) as well as a crude protein ratio close to (Ţîţei, 2021) or intermediate crude protein content (Ţîţei, 2018) compared to important forage legumes such as *Onobrychis viciifolia* and *Medicago sativa*. The forage of *C. varia* (Ţîţei, 2021), a species with high relative feed value, has a higher optimum mineral content compared to *O. viciifolia* (Ţîţei, 2018). Additionally, *C. varia* has a lower methionine content than *M. sativa* and a higher methionine content than *O. viciifolia*; and higher asparagine, glutamine, proline, glycine and alanine content than both species (Ţîţei, 2018). *Coronilla* species which are many of them are considered as forage plants due to their medium and/or good feed quality properties, are also important components of traditional medicine due to the secondary metabolites that they contain. Previous research in *Coronilla* sp. has revealed the presence of several bioactive compounds in different parts of the plant, including the seeds.

2.1. Coumarins

Coumarins have gained importance in recent years due to their various biological/pharmacological activities, especially anticancer activity; in this sense, both natural and synthetic coumarin derivatives have drawn an attention (Küpeli Akkol et al., 2020). Due to their presence in the structure of many plants, especially legumes, their abundant sources and easy synthesis have led researchers to focus on coumarins (Wu et al., 2020). Many species of *Coronilla* are known to produce various compounds with pharmaceutical effects, such as coumarin.

Four hydroxycoumarins have been isolated from *C. elegans* Panc., of which isoscopoletin (6-hydroxy-7-methoxycoumarin) was the first to be isolated from the genus *Coronilla* (Kovalev and Komissarenko, 1984).

Again, in some *Coronilla* species [*C. vaginalis* Lam., *C. scorpioides*, *C. viminalis* Salisb., *C. orientalis*] the hydroxycoumarins umbelliferone, scopoletin, and daphnoretin were detected. Moreover, the dihydrofurocoumarin marmesin is found only in the bound form in the leaves and roots of *C. scorpioides* and *C. vaginalis*. Also in these two species the furocoumarin psoralen was detected in all the plant parts in both free and bound forms (Komissarenko and Zoz, 1969; Innocentp et al., 1989; Innocenti et al., 1996; Piovan et al., 2014). Coumarins have also been isolated from *C. varia* (Komissarenko, 1969; Kovalev and Komissarenko, 1983; Opletal et al., 1998), *C. hyrcana* Pril., *C. cretica* L. and *C. orientalis* (Komissarenko, 1969), and *C. repanda* Guss. (Komissarenko et al., 1969a). Some coumarins in *Coronilla* species are given in Figure 2.

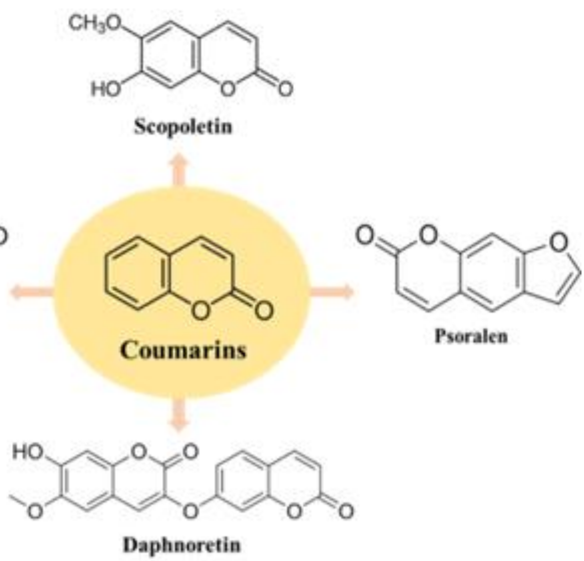

Figure 2. Chemical structure of some coumarins found in *Coronilla* species

2.2. Cardiac Glycosides

Cardiac glycosides (CGs) are naturally occurring bioactive compounds (Menezes et al., 2018; Rimpelová et al., 2021). Most CGs are potent inhibitors of Na^+/K^+-ATPase, and some are routinely utilized in the treatment of various cardiac conditions. The anticancer potential of some CGs compounds has also been identified (Rimpelová et al., 2021).

Cardenolide glycosides (hyrcanoside, hyrcanogenine, coronillin, corotoxigenin, frugoside, glucocorotoxigenin, scorpioside, and coronillobioside), which are pharmaceutically interesting compounds, are found in *C. scorpioides* and *C. repanda* species (Strizhova-Salova, 1957; Komissarenko et al., 1969a; Piovan et al., 2014). From the seeds of *C. scorpioides* a new cardenolide glycoside has been obtained which has been called scorpioside and which has the structure of 3-*β*-(*β*-D-glucofuranosyloxy)-5, 14*β*-dihydroxy-19-oxo-5*β*-card-20-enolide (Komissarenko et al., 1969b).

Hyrcanoside is a secondary plant metabolite of *C. varia* (Rimpelová et al., 2021). Mraz et al. (1992) isolated hyrcanoside and deglucohyrcanoside from *C. varia* seeds. Hyrcanoside, deglucohyrcanoside (Figure 3), hyrcanogenin, and substance E compounds were isolated from the seeds of another species, *C. hyrcana* (Bagirov and Komissarenko, 1966).

Securigera securidaca (L.) Degen & Dörfl. (Synonym: *Coronilla securidaca* L., *Securigera coronilla* DC.) three cardiac glycosides (Securigenin-3-*O*-β-glucopyranosyl-(1→4)-β-xylopyranoside, securigenin-3-*O*-inositol-(1→3)-β-glucopyranosyl-(1→4)-β-xylopyranoside and securigenin-3-*O*-α-rhamnopyranosyl-(1→4)-α-glucopyranoside) were isolated from their seeds (Tofighi et al., 2017).

Similarly, the cardiac glycoside hyrcanoside has been isolated from *Coronilla* species such as *C. varia*, *C. hyrcana*, *C. cretica* and *C. orientalis* (Komissarenko, 1969; Williams and Cassady, 1976).

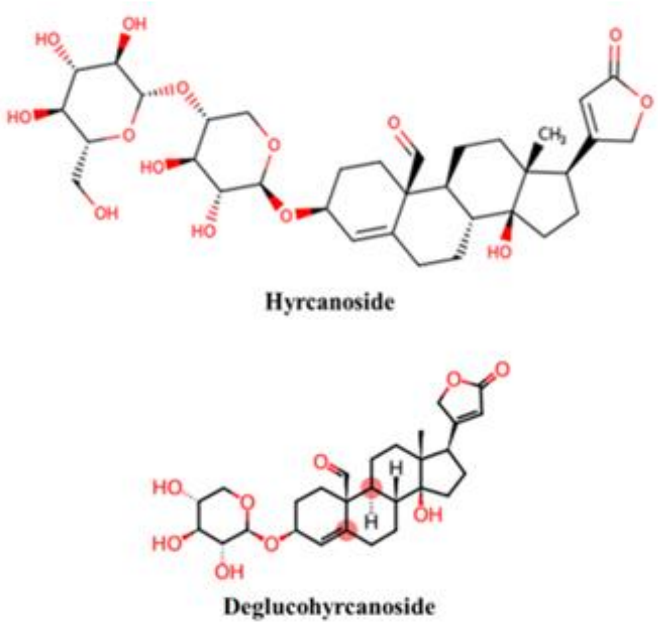

Figure 3. Examples of cardiac glycosides

2.3. Flavonoids

Flavonoids are an important class of natural substances, with polyphenolic structure, characterized by a general structure consisting of two benzene rings (two phenyl rings and a heterocyclic ring) (Ciumărnean et al., 2020). Flavonoids, a secondary metabolite found in the natural structure of plants, are polyphenolic compounds that have strong antioxidant properties (Ma et al., 2024b) and are responsible for many pharmacological activities/functions, especially anti-inflammatory, antiviral, anticancer, antimicrobial and cardioprotective (Liga et al., 2023). Flavonoids are found in the roots, stems, leaves and fruits of many plant species (Liu et al., 2024). The presence of flavonoids in *C. varia* has been widely reported. Many scientists have isolated flavonoids from this plant.

One new (isoorientin 2″-*O*-rhamnoside) and five known (isovitexin, isoorientin, isovitexin 4′-*O*-glucoside, isoorientin 4′-*O*-glucoside, and isoorientin 7-*O*-glucoside) flavone C-glycosides were isolated from leaves and stems of *C. varia* (Sherwood et al., 1973). In addition, some flavonoids such as kaempferol, astragalin, trifolin, saponaretin, and homoorientin were isolated from the aerial parts of *C. varia* (Komissarenko et al., 1989). Flavonoids such as isovitexin and isoorientin (Geuder et al., 1997) were identified in *C. varia* leaves, kaempferol and astragalin (Bodalski and Rzadkowska-Bodalska, 1966) in inflorescences, and isoflavone compounds called genistin and genistein (Hanganu et al., 2010) were identified in the same plant.

Three flavonoid glycosides (orobol-4′--*O*-glucopyranoside, isorhamnetin 3-*O*-neohesperidoside, and isosalipurposide) were isolated from the seed extract of the *S. securidaca* species (Tofighi et al., 2014). In another study conducted with *S. securidaca*, isoquercetrin (3340 mg/100g), naringin (19.73), hesperidin (32.09), luteolin (10.24), quercetin (1.16), kaempferol (0.62), catechin (39.44) and hesperetin (0.10) flavonoids were defined in the flowers (Ibrahim et al., 2015). Some flavonoids in *Coronilla* species are given in Figure 4.

By Sientzoff et al. (2015) one new and twelve known flavonoid glycosides together with three nitropropanoylglucopyranoses were isolated, including astragalin, kaempferol-3-*O*-(6-*O*-acetyl)-β-D-glucopyranoside, kaempferol-3,4′-di-*O*-β-D-glucopyranoside, trifolin, isoquercitrin, hyperoside, isovitexin, isoorientin, isovitexin 4′-*O*-β-D-glucopyranoside, apigenin 7-*O*-β-D-glucuronopyranoside, luteolin 7-*O*-β-D-glucuronopyranoside, apigenin 7-*O*-α-L-rhamnopyranosyl-(1→2)-β-Dglucuronopyranoside, apigenin 7-*O*-β-D-glucopyranosyl-(1→2)-β-

D-glucuronopyranoside, 6-*O*-(3-nitropropanoyl)-β-D-glucopyranoside, coronillin and coronarian in *S. varia*.

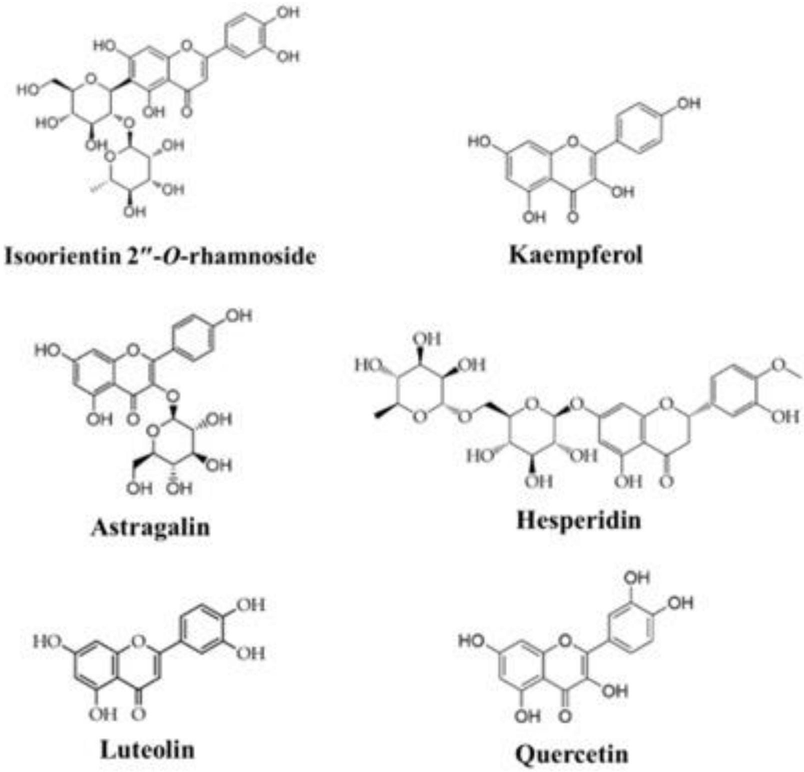

Figure 4. Chemical structure of some flavonoids found in *Coronilla* species

Yerlikaya et al. (2021) determined the content of flavonoids in the ethyl acetate extract (EAE) of *C. varia* as 25.66 mg RE/g (RE: Rutin equivalent). In this study, the presence of isoflavonoids such as isoquercitrin, isorhamnetin-3-O-glucoside, isorhamnetin and uralenneoside in *C. varia* was described for the first time. In the same study, quercetin-3-O-glucuronide, quercetin-O-pentosyldeoxyhexosylhexoside, rutin, isorhamnetin-O-hexosylhexoside, naringenin-6,8-di-C-glucoside, tetrahydroxy(iso)flavone-O-glucuronide, dimethoxy-tetrahydroxy(iso)flavone isomers, quercetin and quercetin-O-pentoside were detected in different extracts.

Kaempferol glycoside, a member of the flavonoid group, was isolated from the leaves and flowers of *C. emerus* and identified as 3-glucoside-7,4′-dirhamnoside (Harborne and Boardley, 1983). The antioxidant and antimicrobial activities of the *C. parviflora* Moench plant have been attributed to the phenol and flavonoid compounds found in the plant metabolites (Uçar Sözmen et al., 2022).

Some other phytochemical studies have also indicated the presence of flavonoids in *C. varia* (Joo et al., 1975; Buchvarov et al., 1977; Noori, 2012), *S. securidaca* (Behbahani et al., 2013; Ibrahim et al., 2015; Abdelbagi et al., 2023), *C. minima* L. (Ferrante et al., 2020), *C. juncea* L. (Kherkhache et al., 2024) species.

2.4. Phenolics

Phenolics are a heterogeneous group of natural substances characterized by an aromatic ring containing one or more hydroxyl groups (Bärlocher and Graça, 2020). Among secondary metabolites, phenolic compounds have significant physiological roles in plants (Ahlawat et al., 2024). At the same time, phenolic compounds are of great importance due to their various beneficial biological activities, including antioxidant, anti-inflammatory, antitumor, and antimicrobial properties. The type and amount of phenolics in plants may vary depending on plant species and different plant parts of the same species.

In *C. varia*, scopoletin (7-hydroxy-6-methoxycoumarin), umbelliferone (7-hydroxy-coumarin), *p*-coumaric acid (trans-4-hydroxy-cinnamic acid), *o*-coumaric acid (trans-2-hydroxycinnamic acid)), leuco-anthocyanins (flavan-3-4-diols) and catechin compounds (flavan-3-ols), ferulic acid phenolic compounds were determined (Joo et al., 1975). In other studies conducted with *C. varia*, the highest total phenolic content (TPC) of the plant was found as 50.86 mg GAE/g (GAE: Gallic acid equivalent) in EAE (Yerlikaya et al., 2021) and 15.06 mg GAE/g according to the Folin-Ciocalteu modified method (Obistioiu et al., 2021).

Securigera securidaca flowers contain 8 phenolic acids [trans-cinnamic acid (2.36 mg/100g), salicylic acid (15.54), protocatechuic acid (34.40), ellagic acid (13.47), caffeic acid (5.40), chlorogenic acid (8.42), *p*-coumaric acid (7.58) and gallic acid (0.95)] were determined (Ibrahim et al., 2015).

In the study conducted with *C. juncea*, TPC contents in roots, stems, flowers and seeds were determined as 31.41-99.23, 44.22-140.91, 40.52-133.55 and 35.43-126.20 mg GAE/g, respectively (Kherkhache et al., 2024). It was also found that the *C. minima* species is rich in phenol content (Ferrante et al., 2020).

2.5. Condensed Tannins

Condensed tannins (CTs) (also known as proanthocyanidins) are secondary plant polyphenol compounds that are considered anti-nutritional due to their protein-binding ability (Kelln et al., 2020). CTs are more abundantly found in plants than hydrolysable tannins and have a more complex structure (Cai et al., 2017). Interest in legumes containing CT has increased due to their anthelmintic properties (Min and Solaiman, 2018; Mueller-Harvey et al., 2019). Condensed tannins can be found in leaves, roots, wood, bark, fruit, buds, and flowers (Kraus et al., 2003).

A condensed tannin concentration of 16.0 g/kg was determined in *C. varia* dry matter (Terrill et al., 1992). In another study, Douglas et al. (1993) determined the extractable CT in whole plants of *C. varia* to be between 65.5-72.5%, and the total CT ratio in lamina and stem was determined as 3.00% and 0.63%, respectively. In the same species, Tanner et al. (1994) pointed out the presence of proanthocyanidins. Condensed tannin contents in *C. orientalis* and *C. parviflora* species were determined as 3.78 and 103.78 mg/kg DM, respectively (Gurbuz, 2009).

2.6. Terpenoids

Terpenoids, the most abundant compounds in natural products, are a set of important secondary metabolites in plants with diverse structures (Yang et al., 2020). Terpenoids have pharmacological activities such as antitumor, anti-inflammatory, antibacterial, antiviral, antimalarial, anti-proliferative, apoptotic, anti-angiogenic, anti-metastatic, and hypoglycemic (Yang et al., 2020; El-Baba et al., 2021).

Terpenoids have been isolated from all plant parts of *Coronilla* species. In the extracts obtained by solid phase microextraction (SPME) technique, limonene (43.4%) in *C. orientalis*, (*Z*)-*β*-ocimene and (*E*)-*β*-ocimene (34.3% and 32.4%) in *C. varia* were identified as the main compounds. In the same study, it was determined that *C. orientalis* essential oil was rich in γ-terpinene (22.4%) and *C. varia* essential oil was rich in phytol (30.7%) (Renda et al., 2019). The GC-MS analysis of the essential oil of the *C. varia* the major components were determined caryophyllene oxide (60.19%), alphacadinol (4.13%) and homoadantaneca robexylic acid (3.31%) (Dehpour et al., 2014).

2.7. Other Specific Compounds

The aerial parts of *C. varia* were isolated three new 3-nitropropanoyl-D-glucopyranoses, 2,3,6-tri(3-nitropropanoyl)-α-D-glucopyranose (corollin), 1,2,6-tri(3-nitropropanoyl)-α-D-glucopyranose (coronillin) and 2,6-di(3-nitropropanoyl)-α-D-glucopyranose (coronarian) (Moyer et al., 1977). In *C. varia*, the presence of organic compounds such as cyanidin, delphinidin, carbohydrates such as glucose and galactose (Joo et al., 1975); some important compounds such as vitamin B5, riboflavin, citric acid, medicarpin (isoflavonoid derivative), and noscapine (alkaloid) (Yerlikaya et al., 2021) have been documented.

Uçar Sözmen et al. (2022) determined that the main component of the methanol extract of *C. parviflora* flowers was "palmitinic acid" (20.85%) and the main component of the water extract was "4H-Pyran-4-one, 2,3-dihydro-3,5-di hydroxy-6-methyl" (23.72%).

Securigera securidaca methanol extract was found to have 27 natural compounds that constituted 99.5% of its total composition. In this research, many phytochemicals, mostly consisting of aromatics and oxygenated hydrocarbons, were documented according to HPLC-PDA (High Performance Liquid Chromatography-Photodiode Array Detector) results of *S. securidaca*. In the same study, dodecanedioic acid and its derivatives and *β*-Sitosterol were reported to be pharmacologically active components not previously reported in this plant (Aldal'in et al., 2020).

3. TRADITIONAL USE OF *Coronilla* sp.

Plant secondary metabolites have been used in traditional medicine for centuries due to their broad biological activities (Ahlawat et al., 2024). *Coronilla* species have been applied in traditional eastern medicine to various disorders such as epilepsy, hypertension, malaria, gastric influx, and hyperlipidemia, due to the secondary metabolites they contain. Furthermore, it has long been used in traditional medicine for treating cold, diabetes, pain, and as cardiotonics (Ferrante et al., 2020). *Securigera securidaca* is widely used as an antidiabetic and antihyperlipidemic drug in Iranian, Jordanian, Indian and Egyptian folk medicine (Porchezhian and Ansari, 2001; Tofighi et al., 2014, 2017; Ibrahim et al., 2015; Aldal'in et al., 2020).

In his work "De Materia Medica", Dioscorides mentions that he treated a person who was stung by a scorpion using the *C. scorpioides* plant, which has small leaves and seeds similar to the tail of scorpions (Arıkan, 2022).

In Türkiye, in Afyonkarahisar and its surroundings, *C. varia* subsp. *varia* flower and leaf parts are used in the form of tea as a sedative for respiratory distress diseases (Arı, 2014); the dried flowers of *C. orientalis* Miller var. *orientalis* (All.) Vitman are crushed and used in the treatment of boils (Goc et al., 2021), and young leaves are used in the Iğdır region for kidney and tonsillitis (Altundağ, 2009).

4. PHARMACOLOGICAL ACTIVITIES OF *Coronilla* sp.

Coronilla contains various bioactive compounds such as coumarins, cardiac glycosides, flavonoids, phenolics, condensed tannins and terpenoids. The bioactivities of *Coronilla* sp. are attributed to these chemical constituents. In this sense, there are important findings regarding the evaluation of different pharmacological effects of various plant parts of *Coronilla* species.

4.1. Antioxidant and Free Radical Scavenger Activities

Since the *Coronilla* genus is from the Fabaceae family, it is a potential antioxidant source that can be used in deep pharmacological research. In the *Coronilla* genus, 2-2'-diphenyl-1-picrylhydrozyl (DPPH) scavenging activity may vary depending on the species and different parts of the plant.

The methanol extract of aerial parts of *Securigera varia* L. (Synonym: *Coronilla varia*) showed a significant DPPH radical scavenging effect with an EC50 value of 92.6 µg/mL. The main secondary metabolites of the plant that play a role in this antioxidant effect are flavonoids (Sientzoff et al., 2015). In *C. varia*, the free radical scavenging activity of methanol extracts of the whole above-ground part was 62.78%, while this rate was determined to be in the range of 50-60% in the water extract. In the same study, DPPH scavenging activity was determined as 87.05% in methanol extracts of leaves and 57.62% in water extracts; around 80% in methanol extracts of inflorescences and 65.54% in water extracts; 35.04% in methanol extracts of stems and 20.35% in water extracts (Vergun et al., 2020). In the research conducted on different parts extracts of *C. varia*, strong antioxidant capacity was reported in methanol (20.35 µg/mL) and water (35.04 µg/mL) stems extracts (Khalil et al., 2022).

Another *Coronilla* species, *Coronilla juncea*, has significant free radical scavenging property. It was determined that the antioxidant activity evaluated by the DPPH test in *C. juncea* varied according to different parts of the plant, that the antioxidant activity of various parts extracts decreased in the order of flowers> stems> roots> seeds, and that the scavenging effects of all flower and stem extracts were excellent. Researchers also attributed the difference in antioxidant activities to the diversity of phytochemical components of *C. juncea* (Kherkhache et al., 2024).

A study was conducted by Uçar Sözmen et al. (2022) to test the antioxidant activities of *C. parviflora* extracts. For this purpose, *C. parviflora* flowers were extracted in water and methanol. Afterwards, the activity of each extract was determined using in vitro DPPH and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical scavenging activity method. According to the data obtained from the DPPH method, the antioxidant activity of the methanol extract of *C. parviflora* flowers was found to be better than the water extract.

It was determined that essential oils, chloroform, ethyl acetate, methanol, and water extracts of *C. orientalis* and *C. varia* species have moderate DPPH radical scavenging activities (Renda et al., 2019). In a different study, the effectiveness of *C. minima* as an antioxidant agent was emphasized (Ferrante et al., 2020).

4.2. Anticancer Activity

Cancer is considered the end stage of a chronic disease process characterized by abnormal cell and tissue differentiation (Sporn and Suh, 2000). For centuries, people have used herbal medicines to treat various diseases. For this reason, in recent years, research has focused on new plant species that show biological activity against cancer types in addition to modern medicine. The *Coronilla* genus has significant potential as plant material within these plant groups.

Ethyl acetate extract and methanol extract of the *C. varia* plant were found to suppress cell migration by inhibiting metastatic activity in MDA-MB-231 and MCF-7 breast cancer cells (Yerlikaya et al., 2021). Some other research data on the anticancer activity of the *C. varia* plant (Dehpour et al., 2014; Rimpelová et al., 2021) are also available.

Cyclin-dependent kinase 1 (CDK1) is a key regulator of the cell cycle and is frequently dysregulated in cancer, this makes it a promising target for anticancer therapy (Abdelbagi et al., 2023). In a study examining the seeds of *S. securidaca*, traditionally used in folk medicine for various ailments including cancer, it was reported that hippeastrine and naringenin detected in the plant were identified as promising compounds for CDK1 inhibition and that this plant may offer new opportunities for the development of effective anti-cancer agents (Abdelbagi et al., 2023).

4.3. Antitumor Activity

In studies conducted with some species of the *Coronilla* genus, for example, *C. varia* (Williams and Cassady, 1976; Hembree et al., 1979; Al-Snafi, 2016) and *C. scorpioides* (Amal et al., 2009; Al-Snafi, 2016) have been reported to exhibit antitumor activity due to their cardiac glycosides content.

4.4. Antimicrobial Activities

Extracts obtained from the aerial parts of *C. varia* have been reported to have strong antibacterial activity against gram-negative bacteria (Usta et al., 2014).

In a research representing the first biopharmacological investigation on *C. minima*, the antimycotic effects of water (H_2O) and hydroalcoholic (Et-OH/H_2O) extracts of the plant covering different temperatures and durations were found to be positive in *Candida albicans* and *Aspergillus minutes* cultures. In the same study, hydroalcoholic extract was effective in inhibiting the growth of *Bacillus cereus* (Ferrante et al., 2020). Some other studies have also emphasized the antibacterial (Dehpour et al., 2014) and antimicrobial (Obistioiu et al., 2021) activities of *C. varia*.

4.5. Antiviral Activity

There are limited studies on this pharmacological activity with the *Coronilla* plant. It has been shown that kaempferol and kaempferol-7-O-glucoside compounds isolated from *S. securidaca* exhibit an effective inhibitory mechanism in the early stage of HSV-1 infection (Behbahani et al., 2013).

4.6. Hypoglycemic Activity

The hypoglycemic activity of the *S. securidaca* species has been documented. In the study, cardiac glycosides contained in the plant seeds were reported as the compounds responsible for this activity. These cardiac glycosides have been shown to reduce blood sugar due to the increase in insulin level, thus providing a logical explanation for the use of *S. securidaca* as traditional medicine (Tofighi et al., 2017). The antihyperglycemic activity of *S. securidaca* seeds has also been confirmed by various other in vivo studies (Porchezhian and Ansari, 2001; Hosseinzadeh et al., 2002; Zahedi et al., 2005; Pouramir et al., 2011). Another study confirmed the use of *S. securidaca* flowers as antidiabetic agents. It has been reported that this activity of the species is due to its high phenolic content (Ibrahim et al., 2015). Antidiabetic activities in the same plant were also reported by Minaiyan et al. (2003), Ahmadi et al. (2016), and Aldal'in et al. (2020).

4.7. Other Pharmacological Activities

Coumarins are phytochemicals with a wide spectrum of biological activities, including acetylcholinesterase (AChE) inhibition (Anand et al., 2012). Coumarins may play a role, which are predominantly found in *Coronilla* species, in AChE enzyme inhibition (Anand et al., 2012), an important target for the management of Alzheimer's disease.

Essential oils of *C. orientalis* and *C. varia* species were found to have significant AChE and butyrylcholinesterase (BuChE) inhibitory activities (Renda et al., 2019). In the pharmacological evaluation of *C. varia* extracts, it was reported that this plant exhibited cytotoxic effects due to secondary metabolites (Dehpour et al., 2014). Additionally, the effectiveness of *C. minima* as an antiproliferative agent has been emphasized (Ferrante et al., 2020). Mraz et al. (1992) reported that cardenolide glycosides found in *C. varia* exhibited remarkable cardiotonic activity (Na^+, K^+-ATPase inhibitory activity).

Antilipidemic (Garjani et al., 2009; Ibrahim et al., 2015; Ahmadi et al., 2016; Aldal'in et al., 2020), antiulcerogenic (Mard et al., 2008), anti-nociceptive (Shahidi and Pahlevani, 2013), anti-inflammatory (Ahmadi et al., 2019) effects of *S. securidaca* plant have been reported.

5. CONCLUSION

Coronilla sp. is distributed in the Mediterranean region, Asian and European countries and the northern parts of Africa. Phytochemical studies on *Coronilla* species have shown that the main bioactive components of these plants are coumarins, cardiac glycosides, flavonoids, phenolics, condensed tannins and terpenoids. The biological activities and medicinal properties of *Coronilla* species depend on these secondary metabolites present in different parts of the plant. In this sense, it has been documented that *Coronilla* species exhibit antioxidant, anticancer, antitumor, antimicrobial, antiviral and hypoglycemic activities, as well as antilipidemic, antiulcerogenic, anti-nociceptive, anti-inflammatory, antiproliferative and cardiotonic activities and cytotoxic effects.

Numerous species of *Coronilla* may be valuable agents in natural therapy to design new pharmaceutical compounds. For all that, further studies are needed to determine the exact mechanisms and main bioactive compounds responsible for treating specific diseases.

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CHAPTER IV

BRASSICA SPECIES AS MEDICINAL PLANTS

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INTRODUCTION

Medicinal plants were the first source of treatment, and they have been utilised in traditional medicine for thousands of years in many nations (Khan, 2014). Human organisations have been spreading empirical proof of their positive impacts across time (Bhat, 2021).

If a plant has substances in one or more of its organs that are valuable for medicine or that may be used to manufacture additional useful medications, then the plant is considered medicinal. According to Sofowora et al. (2013), this definition can make it simple to differentiate between plants that have been demonstrated via research to possess therapeutic qualities and ingredients and those that are believed to be medicinal but have not yet been the subject of in-depth scientific study. Any plant that "contains substance that can be used for therapeutic purposes, or which are precursors for chemo-pharmaceutical semi-synthesis" is deemed "medicinal" (Zhang, 2002).

Global food supply are based on brassica plants, which are farmed alongside cereals. They stand out from other vegetable plants due to their excellent nutritional value, which includes low protein and fat content and high levels of vitamins, fibre, and minerals. They also include a variety of phenolic compounds and glucosinolates, a special kind of compound that sets these crops apart from other vegetables. These substances also give the genus Brassica a variety of biological activity (Salehi et al., 2021).

1. IMPORTANCE OF BRASSICA SPECIES AS MEDICINAL CROPS

Plants belonging to the genus Brassica are the most widely consumed vegetables worldwide. Within a group of six related species of global economic importance, this genus has three diploid species: *Brassica carinata* A. Braun, *Brassica juncea* (L.) Czern., and *Brassica napus* L. are the three amphidiploid species. These consist of Brassica rapa L., *Brassica oleracea* L., and *Brassica nigra* (L.) K. Koch. These types are divided into oily, feed, spice, and vegetable groups based on their physical traits, chemical composition, and the utility of their plant parts. Human clinical studies are crucial, as are the habitat, phytochemical makeup, and bioactive potential of Brassica plants—particularly their antibacterial, antioxidant, and anticancer qualities (Salehi et al., 2021).

Due to the strong, sharp flavour of its primary metabolites, glucosinolates (GLSs), which include sulphur, Brassicaceae are sometimes referred to as the "mustard" (from the Latin mustum ardens) plant family (Mithen et al., 2010; Björkman et al., 2011).

In the Brassicaceae family, mustard members were the first to be grown (Rahman et al., 2018). The diverse family Brassicaceae, usually known as crucifers, comprises 338 genera and about 3,700 species (Ahuja et al., 2010). Brassica plants are thought to be the oldest cultivated plants that humans have known about since 1500 BC. Medicinal plants are an excellent source for the development of new medications, either as an extract or as a pure compound (Shah et al. 2017).

The importance of Brassica plants in medicinal use will be discussed in detail.

2. INTERSPECIFIC RELATIONSHIPS OF MAIN BRASSICA SPECIES (Triangle of U.)

Before discussing the importance of Brassica species it would be necessary to take a view to the relationships of main Brassica species.

The most significant genus is Brassica, which includes a variety of vital vegetables and oil crops, including rapeseed, kale, cauliflower, broccoli, and cabbage. Nearly all of these economically significant plants are members of the six cultivated species: *Brassica napus*, *Brassica rapa*, *Brassica juncea*, *Brassica nigra*, *Brassica carinata*, and *Brassica oleracea*.

A well-known model, U's triangle, was put up to illustrate the genetic links among these six species based on artificial inter-specific hybridisation experiments (Figure 1; U, 1935). Natural hybridisation and genome doubling produced three allotetraploid species: *B. juncea* (AABB, 2n = 4x = 36), *B. carinata* (BBCC, 2n = 4x = 34), and *B. napus* (AACC, 2n = 4x = 38). These species are basic diploids, *B. rapa* (AA, 2n = 2x = 20), *B. nigra* (BB, 2n = 2x = 16), and *B. oleracea* (CC, 2n = 2x = 18).

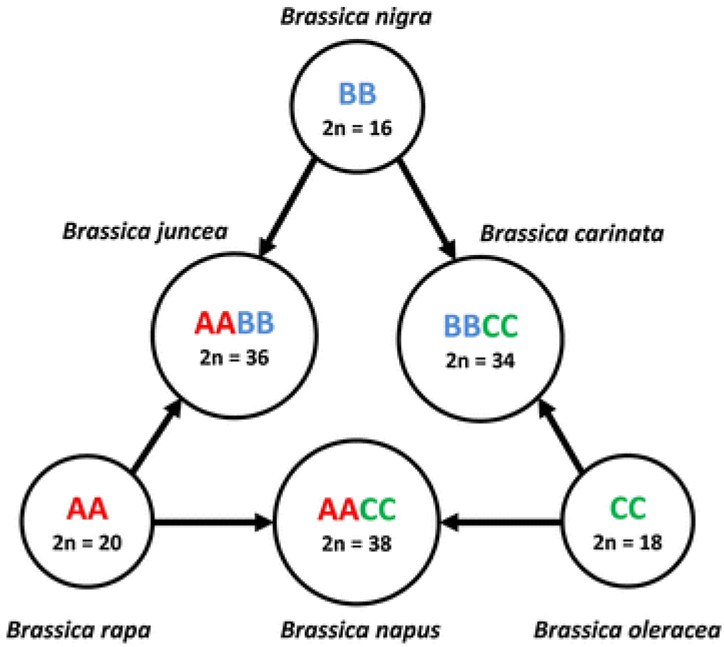

Figure. 1. U.N. (1935) : Relationships of *Brassica* species

It is possible to transfer a character found in one species to other related Brassica species due to potential interspecific crosses (U, 1935).

3. MEDICINAL USES OF BRASSICA PLANTS

The Brassica genus is known for its glucosinolates and phenolic chemicals, which also contribute to a variety of biological features (Petropoulos et al., 2017). As a result, these qualities have been used in various traditional medicine applications around the world. Seven Brassica species, including *B. juncea*, *B. napus*, *B. nigra*, *B. oleracea*, and *B. rapa*, are the most often utilised in traditional medicine. The most common applications of Brassica plants in traditional medicine are summarised in Figure 2. Brassica plants are also employed in veterinary therapy for livestock (Kumar and Bharati, 2013).

Figure 2. Traditional medicinal use of Brassica plants [Colour figure can be viewed at wileyonlinelibrary.com]

4. BRASSICACEAE FAMILY: A RICH MINE OF BIOACTIVE PHYTOCHEMICALS

Vegetables from the Brassicaceae family are widely distributed throughout the planet, with the exception of Antarctica. One of the most distinguishing characteristics of this botanical family is the presence of a variety of secondary metabolites with different flavours as well as intriguing bioactivities. The most extensively researched are the glucosinolates (GSL) and their breakdown products, isothiocyanates and indoles (Argento et al., 2019; Branca et al., 2013;

Galletti et al., 2015). Furthermore, these species are diverse and have distinct profiles of phenolic compounds, carotenoids, and other less researched chemicals such as phytoalexins, terpenes, phytosteroids, and tocopherols.

In Figure 3, the chemical structure of the phenolic compounds usually present in Brassicaceae is shown.

Known for its anti-inflammatory, antihypertensive, vasodilator, antiobesity, antihypercholesterolemic, and antiatherosclerotic properties, quercetin is one of the significant bioflavonoids found in over twenty plant materials (Salvamani et al., 2014; Sultana and Anwar, 2008).

Fruits and vegetables contain the polyphenol antioxidant kaempferol. Dietary kaempferol has been shown in numerous studies to have positive benefits on lowering the risk of chronic illnesses, particularly cancer (Chen and Chen, 2013).

A prevalent phytochemical in fruits and vegetables like rice bran, sweet corn and tomatoes is ferulic acid (FA). It results from the Shikimate pathway's metabolism of phenylalanine and tyrosine in plants. It has a broad spectrum of therapeutic effects against a number of illnesses, including diabetes, cancer, heart disease, and neurological disorders (Srinivasan et al., 2007).

Numerous chronic diseases, including cardiovascular diseases (CVDs), cancer, liver diseases, obesity, diabetes, Alzheimer's disease, and Parkinson's disease, can be prevented by resveratrol because of its antioxidant, anti-inflammatory, immunomodulatory, glucose and lipid regulatory, neuroprotective, and cardiovascular protective properties (Meng et al., 2020).

Gallic acid has been shown to have a number of positive effects, such as anti-inflammatory, antioxidant, and anti-cancer effects. According to reports, this chemical has therapeutic properties for metabolic, cardiovascular, cognitive, and gastrointestinal diseases (Kahkeshani et al., 2019).

Furthermore, one of the largest groups of naturally occurring anthocyanins is cyanidin and its glycosides; their biological and antioxidant qualities have been thoroughly studied (Galvano et al., 2004).

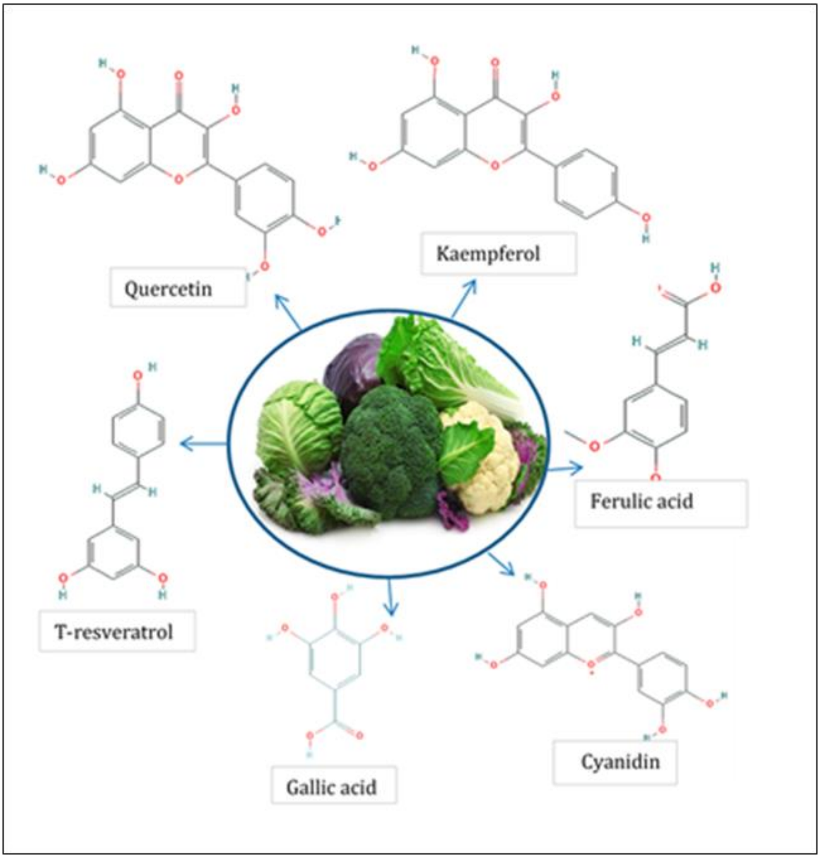

Figure 3. Phenolic compounds present in members of Brassicaceae (Fusari et al., 2019)

5. DIFFERENT BRASSICA PLANTS USED IN TRADITIONAL MEDICINE

Brassica plants and their parts used in traditional medicine are listed in Table 1. We can see from Table 1 that different organs of different Brassica species reveal potenatials as biochemical agents.

Table 1. Use of Brassica plant in traditional medicine

Brassica Plant	Part	Uses	Reference
Brassica juncea (L.) Czern. (Oriental mustard)	Leaves and seeds	Arthritis, foot-ache, lumbago, diuretic, emetic, rubefacient, stimulant, and rheumatism	Rahman et al. (2018)
	Seeds	Oil is used as tonic along with onion. Used externally to children for ascariasis. Treatment of Infections in tail of livestock.	Kumar and Bharati, 2013; Shah et al. (2016)
	Leaves	Hypoglycemic effect (stimulation of glycogen synthetase)	Grover et al. (2002)
Brassica napus L.	Seeds	Retention of placenta and umbilical cord after delivery, infection in tail, itching of skin (veterinary medicines)	Kumar and Bharati (2013)
	Root, leaves	Abscess, furuncle, acne, eczema, chilblains (used externally)	Gilca et al. (2018)
	Whole plant	Anticancer, antioxidant, analgesic, diuretic and Anti-catarrhal activity, Diuretic, anti-scurvy, anti-inflammatory of bladder and anti-goat	Amri (2014), Mahmudur et al. (2018), Gohari and AR. (2012)
Brassica nigra (L.) K.Koch (Black mustard)	Seeds	Common cold, painful joints and muscles, arthritis, stimulant, irritant, emetic and to treat bronchitis	Jazayeri et al. (2014); Rahman et al. (2018)
	Aerial part	Cough treatment	Güler et al. (2015)

Table 1. Use of Brassica plant in traditional medicine (continued)

Brassica Plant	**Part**	**Uses**	**Reference**
	Aerial part	Cough treatment	Güler et al. (2015)
Brassica oleracea L. (Broccoli)	Leaves	Cardiac diseases and blood purification, inflammation of any body part, rheumatic pains, contusions, wounds, Skin diseases	Emran et al. (2015); Guarrera (2005); Munns (2003); Tuttolomondo et al. (2014)
	Leaves	Gastric ulcers and also some other diseases such as diabetes mellitus, cirrhosis, and rheumatism	Gonçalves et al. (2012); Lemos et al. (2011)
	Leaves	Wounds, bruise, paronychia, furuncle, abscess, phlegmon, acne, eczema, gangrene, insect/animal bites, skin inflammation, chilblain, skin tumors, scabies, ulcerations, varicose ulcer, herpes zoster, seborrhea	Gilca et al., 2018)
B. oleracea (cauliflower)	Leaves	Antibacterial activity	Prasad (2014)
Brassica rapa L. (Bok choy)	Radish	Tonic and anti-hypoxia, heat-clearing, and detoxification, alleviating fatigue.	Chu et al. (2017)
	Root, leave, and seed	Hypoglycemic	Hassanpour et al. (2015)
	Whole plant	Whole plant is fed to cattle as galactagouge.	Rao et al. (2015)

Table 1. Use of Brassica plant in traditional medicine (continued)

Brassica Plant	Part	Uses	Reference
	Leaves and Seeds	Liniment to relieve aching muscles, disinfect wounds, and in plasters for the remedy of chest congestion and bronchitis.	Rahman et al. (2018)
	Seeds	Treatment and/or management of parasitic diseases of livestock (i.e., helminthic infestation) and remove external parasites, bone fracture and indigestion, to cure hemorrhagic septicemia and galactagogue. Detoxifying the effect of poisonous insect or weed intake (oil from seeds).	Farooq et al. (2008); Hussain et al. (2008); Rao et al. (2015); P. Sharma and Kapoor (2015)
	Pollen	Chronic prostatitis, prostatic hyperplasia, incontinence, as well as for soreness and weakness of waist and knees	Wang et al. (2015); Yang et al. (2013)
	Whole plant	Antiarthritic, antiscorbutic, and resolvent	Duke and Ayensu (1985)
Brassica carinata	Leaves	cancer preventive potential	Odongo et al. (2017)
	Leaves	antibacterial, antioxidant potential	Murugesan et al. (2021)
	Whole plant	Used as bio-fumigant, to suppress soil-borne pests and pathogens Potential as new edible oil/protein crops	Rahman et al. (2018), Warwick (2011)

Reference: Modified from Salehi et al. (2021) and Shankar et al. (2019)

6. OUTLOOK

In contrast to the Western world, 80% of the world's population living in undeveloped areas rely on locally available plant resources for primary healthcare (Shankar et al., 2019). Around 64% of the world's population relies on traditional medicines for treatment.

Brassica's purpose is related to diverse plant parts; for example, seeds provide oil and are used as a condiment, whilst leaves and roots are ingested by humans and animals (Vaughan, 1977). Some Brassica plants have been shown to have anticancer effects (Madhuri & Pandey 2008). Brassica plants play an essential function in Unani medicine. They are useful for preventing gastritis, treating kidney stones, vomiting, and skin infections (Kala et al., 2005).

Additionally, powdered Brassica seeds can be consumed as tea. This tea is excellent against colds, fevers, and influenza (Khare, 2008).

More than 60% of clinically utilised anticancer medicines are natural, with the majority coming from higher plants (Amri, 2014). Cruciferous vegetables are also known for their high quantities of antioxidants such as isothiocyanates, ascorbic acid, carotenoids, and indole-3-carbinol, which may have anticancer characteristics (Amri, 2014; Parkin et al., 2005; Ferlay et al., 2008; Newman et al., 2003). Indole-3-carbinol is a chemical found in Brassica crops that promotes DNA repair while inhibiting cancer cell development. Brassica plants have antiviral, antibacterial, and anticancer effects, as well as the ability to modulate the innate immune system. It also possesses anti-androgenic activities (Shanmuga Sundaram et al., 2020; Vivar et al., 2009).

Because of the given important chemical characteristics of Brassica plants more attention should be directed to their use special work dealing with the use of Brassica species as medicinal agents in Türkiye.

7. CONCLUSION

The Brassica genus (Brassicaceae family) is distinguished by the presence of numerous key species used in gardening and agriculture. Because of their vital dietary components (vitamins and minerals), the majority of Brassica plants are grown for food.

The distinctive flavour and smell are mostly provided by glucosinolates and phenolic chemicals, which also have biological effects such as antioxidant, antibacterial, and anticancer. So far, around 80 natural chemicals from this group have been found. In general, a plant has numerous distinct glucosinolates, each having a unique structure and concentration in specific regions of the plant, particularly the seeds. Furthermore, the quantities of chemical components and antioxidant activity vary according to crop type and cultivar. Vegetables from the Brassicaceae family are abundant in natural antioxidants and have a great ability to combat oxidative stress.

As a result, a greater knowledge of potential mechanisms of action is required to develop more effective prevention and therapeutic measures involving cruciferous vegetables or their components.

Research into raising the levels of phytochemicals in Brassica crops may lead to human intervention to improve food quality. Current study involves interdisciplinary work that integrates the food chain: assessment of edaphic factors, agro-technical factors, pre- and postharvest, all of which have an impact on the phytochemical composition of foods. New food ingredients will find applications in the food sector, and supplementing food with bioactive phytochemicals through sustainable farming techniques will be a priority in clinical interventions for human health. Furthermore, combining nutritional or phytochemical interventions may improve the efficacy of established and developing bladder cancer treatments such immunotherapy, chemotherapy, and radiation, albeit more preclinical evidence and supportive mechanistic investigations are required.

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CHAPTER V

LIGNANS IN FLAX (*Linum usitatissimum* L.) AND THEIR MEDICAL IMPORTANCE

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INTRODUCTION

In recent years, due to reasons such as reducing the risk of getting sick, increasing people's desire to live a healthy life, and increasing awareness of healthy nutrition, consumers want to benefit from many nutrients for health, as well as getting nutrients from foods. Functional foods have gained importance due to the discovery of new ingredients based on developments in science and technology and their association with health, economic reasons and the increase in treatment costs, and people's interest in new products and quality. Functional foods have become a developing sector of the food industry.

Functional foods are food components or foods that, in addition to providing basic nutritional elements to the body, also provide additional benefits on human physiology and metabolic activities. Functional foods create significant effects in protecting against diseases and maintaining a healthier quality of life. These foods make important contributions to protecting against diseases and achieving a healthier life. Among the nutraceuticals known as non-vitamin beneficial chemicals in foods, those of plant origin are called phytochemicals (Başer, 2002).

Nutraceutical foods are often used synonymously with functional foods and include isolated nutrients, nutritional supplements, “designed” foods, herbal products, processed products such as cereals, soups and beverages.

More than 900 phytochemicals have been found in the composition of foods. There is a wealth of *in vivo*, *in vitro* and clinical trial data showing that a diet based on plant products reduces the risk of chronic diseases, especially cancer. Health authorities recommend diets rich in grains, fresh vegetables and fruits, and reduced amounts of animal meat and fat.

For more than 20 years, flax seed has been used as a functional food. Functional foods obtained from flaxseed as flaxseed grain, ground flaxseed, flaxseed oil, flaxseed meal obtained by removing the oil, flaxseed fiber and lignans found in flaxseed are used in the form of extracts (Başer, 2002). Secondary metabolites such as flavonoids, phenolic acids and lignans in the content of flaxseed are natural sources of phytochemicals (Oomah et al ., 1995; Meagher and Beecher ., 2000).

In this sense, the flax (*Linum usitatissimum* L.) plant, which is the plant of life and has been the subject of important research in terms of health, comes to the forefront.

1. FLAX PLANT DESCRIPTION, MORPHOLOGY AND COMPOSITION

1.1. Definition of Linen

Flax belongs to the Linum genus of the Linaceae family. 230 species of of this family have been found and their main distribution areas are North America and the Balkan Peninsula (Hall et al., 2016). It is known that the flax cultivation began in Mesopotamia approximately 10,000 years ago. In ancient Egypt, flax fibers were used for mummification and textile production. Cloths made from flax plant fibers were also used in the construction of the famous Egyptian pyramids. In ancient Greece and Rome, the flax plant was used for health purposes and its fibers were used for many different aims (Crampton and Meudt, 2000).

The flax plant, scientifically known as *Linum usitatissimum* L., is a herbaceous, annual and fiber-containing plant. It mostly grows in cold climates (Sheidai et al., 2019; Saleem et al., 2020). Four main cultural centers have been identified as the homeland of the flax plant, namely the Mediterranean Basin, Southwest Asia, Central Asia and Ethiopia, respectively (Diederichsen and Hammer, 1995; Dash et al., 2017).

When we look at the status of the Linum genus in Türkiye, there are 53 undescribed genotypes. 25 of these genotypes are endemic (Öksüz et al., 2015).

1.2. Morphology of Flax

1.2.1. Root

It has a main taproot structure. It consists of secondary and lateral roots arising from the main root. Taproots are short, lateral roots are few in number and the development of lateral roots is weak (İncekara, 1979).

1.2.2. Stem

The flax plant has a thin, upright and cylindrical stem structure. It is generally green-gray in color. Flax grown for fiber produces a single main stem. Flax planted for oil purposes forms 2-3 side branches, depending on the variety and climatic conditions. In flax plants, tillering occurs from the root crown (Diederichsen and Richards, 2003).

The average plant height of oil flax is 50-80 cm and the stem thickness is 5-6 mm. In fiber flax, the average plant height is 100-120 cm and the stem thickness is 2-3 mm (Gilbertson, 1993).

1.2.3. Leaf

The leaves of the flax plant may be stalkless, lanceolate or spindle-shaped. It has leaf blades measuring 2-5 cm x 0.5-1 cm. It has smooth, shiny, veined and hairless leaves. While fiber flax leaves are small and sparse, oil flax leaves are large and dense (Maiti, 1997).

1.2.4. Flower structure

The flower structure of the flax plant is in the form of a compound panicle. The flax plant continues to bloom as long as it continues to grow.

Flowering occurs from top to bottom. First, the flowers on the main stem bloom, then the second and third degree flowers continue to form on the branches towards the bottom. It has a quintuple flower structure. It has 5 sepals with triangular ends, surrounding the oval capsule. There are 5 petals that can be in violet, blue, pink and white colors. Flax is a self-pollinating plant (Beard and Comstock, 1980).

1.2.5. Fruits and seeds

The fruit of the flax plant is capsule-shaped. The fruits can be round, pointed, long-conical, oval or flat barrel-shaped. Capsules are 5-15 mm long and 5-11 mm in diameter. The capsules are divided into two compartments and there are 5 compartments. A seed is formed in each pod. Flax seeds are small and resemble sesame seeds (Figure 1).

It can be distinguished from sesame seeds by having a protrusion similar to a bird's beak at the tip of the seed and by being more shiny and slippery. Seeds may vary in color and shape depending on the flax variety.

The oil content in flax seeds can vary between 35-45%. The weight of 1000 grains of seeds varies between approximately 4-7 grams. Flax seeds consist of 28-30% protein, 6% minerals and ash and 35% shell (Carter, 1993).

Figure 1. Appearance of seeds, flowers and fruits of *Linum usitatissimum* L.

1.3. Composition of Linseed

When we look at the content of flaxseed, it contains approximately 55% alpha-linoleic acid (ALA), 28-30% protein and 35% fiber. It also contains resin, amygdalin, sugar wax and ash. The ash contains sulphate, potassium, calcium and magnesium chlorides. β-carotene accounts for 22 to 30% of total carotenoids. It contains alpha-linoleic acid (ALA) (52% of total fatty acid) and phenolic compounds commonly known as lignans (>500 μg/g). It contains hydrocolloid gum (about 8% of the seed weight), also known as mucilage, and high-quality protein and fiber (Carter, 1993; Rabetafika et al., 2011).

More than 45% of the oil content in flaxseed consists of omega-3 fatty acids (Yasmeen et al., 2018). Flax seeds are rich in omega-3 fatty acids and are considered an important food source for health due to these properties (Kaur et al., 2018). When we look at the other compounds found in it, there are coumaric acid, lariciresinol, ferulic acid, matairesinol, secoisolarikiresinol and pinoresinol glucoside (Hosseinian and Beta, 2009).

Phenolic compounds (lignans) and other products found in flax plant are used in the treatment of diseases such as high cholesterol, diabetes, vascular and cardiovascular diseases, which are important among the public (Thakur et al., 2009; Rhee and Brunt, 2011).

2. USES OF FLAX PLANT

2.1. Textile Industry

The fibers of the flax plant are known for being durable and light. For this reason, fabrics obtained from the fibers of the flax plant have been widely used in the clothing industry for years. Since the fabric structure of linen contains breathable and cool-keeping properties, it can be used easily in summer months. Nowadays, linen fabrics are frequently found in luxury clothing and home textile products (Young and Atwood, 2002).

2.2. Food and Health

Flax seeds contain nutrients important for health. Flaxseed, which is rich in omega-3 fatty acids, protein, fiber, antioxidants and lignans, has an important place in modern nutrition. Additionally, flaxseed supports the digestive system in terms of health. It lowers cholesterol and plays an important role in the fight against cancer. Since flaxseed oil has a improving effect on skin health, it is also used in beauty products (Lee and Lewis, 2015).

2.3. Industrial Use

Flax plant fibers are one of the important raw materials used in the industrial field. Ropes, cloths and threads made from flax fibers are known for their durability. Linseed oil is used in varnish making in the paint industry and in soap making in the cleaning industry. Recently, it has been used in bioplastic production as an alternative material that is environmentally friendly and sustainable (Parks et al., 2017).

3. MEDICINAL USES OF FLAX SEED

3.1. Digestive System Health

Flax seeds contain high amounts of soluble and insoluble fibers. These fibers improve the digestive system by affecting bowel movements. Soluble fibers soften the stool by retaining water in the intestines, and insoluble fibers help the intestines move regularly. For this reason, flaxseed is used especially for digestive problems such as constipation. By consuming flaxseed regularly and in certain dosages, intestinal health can be supported and digestive system disorders can be prevented (Figure 2)(D'Angelo et al., 2011).

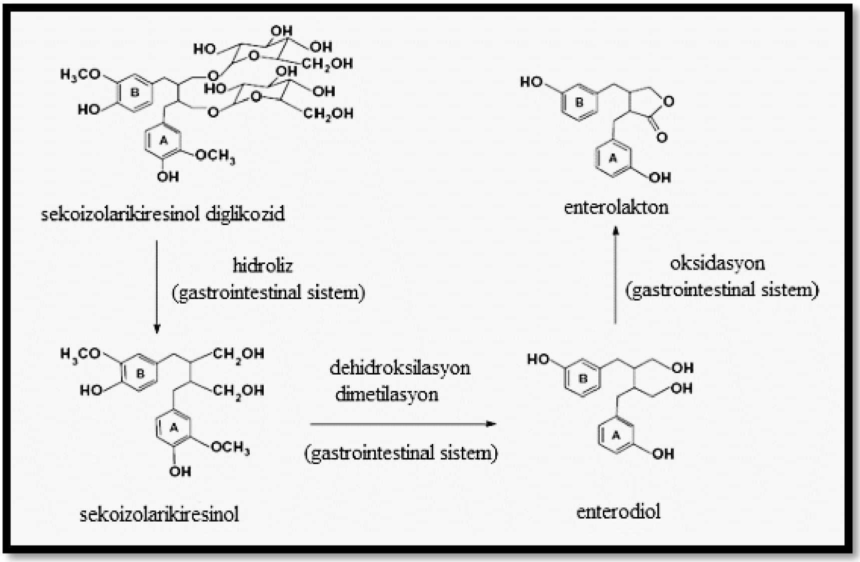

Figure 2. Metabolism of SDG lignan in flaxseed to its aglycone form, SECO, in the large intestine, and then to enterolactone (EL) and enterodiol (ED) mammalian lignans (Hu et al., 2007)

3.2. Fighting Cancer and Hormonal Balance

Flaxseed is very rich in phenolic compounds called lignans. Lignans act like the estrogen hormone and provide protection against cancers caused by hormones. Regular consumption of flaxseeds may reduce the risk of hormone-triggered cancer types such as breast cancer and prostate cancer. Additionally, the antioxidants in flaxseeds can inhibit the growth of cancer cells by fighting free radicals. (Bhatta et al., 2018). Lignans keep hormone levels balanced by acting as a phytoestrogen in the body. Flaxseed may be beneficial for women, especially during menopause (Prasad and Chandra, 2003).

3.3. Skin Health

Due to the omega-3 fatty acids found in flaxseed, it has properties that positively affect skin health. These omega-3 fatty acids are known to reduce inflammation in the skin. It is effective against skin problems such as acne, eczema and psoriasis. Flax seeds improve skin elasticity, increase skin moisture and can postpone the signs of aging (Cakmak et al., 2019).

4. PHENOLIC COMPONENTS (LIGNANS) IN THE STRUCTURE OF FLAXSEED

The reason why flaxseed is important as a functional food is due to the phenolic compounds it contains. The most important members of the phenolic systems groups are lignans. Lignans found in plants are in free form or bound to one or more sugars, that is, in glycoside form. These lignans are found in the seed coat as an ester-linked complex (Muir and Westcott, 2000). The basic structure of lignans is a phenolic secondary metabolite consisting of two phenylpropanoid molecules interlocked with each other. There are two main types of lignans. These types are furanofuran lignans and dibenzylbutane lignans. Examples of lignans are secoisolarikiresinol diglycoside (SDG) in flaxseed and sesamin in sesame seed (Figure 3) (Bakke and Klosterman, 1956; Chimichi et al., 1999). The most abundant lignan in flaxseed is secoisolariciresinol diglycoside (Thompson et al., 2006).

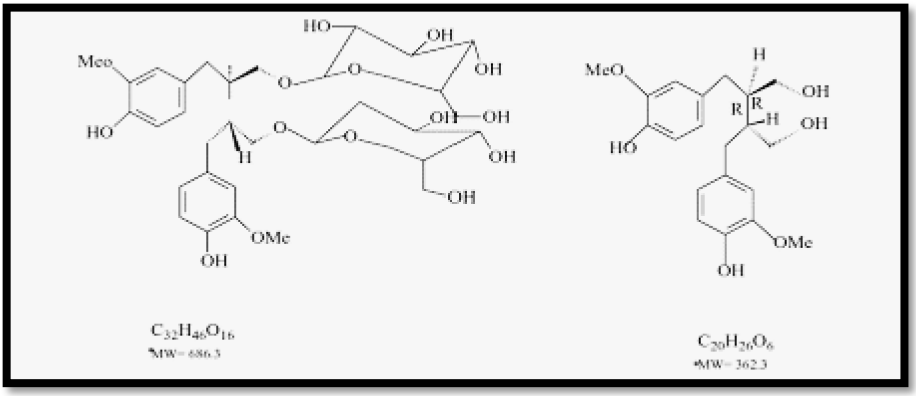

Figure 3. Chemical structures and molecular weights of SDG and SECO compounds (Touré and Xueming, 2010)

Small amounts of components such as pinoresinol, matairesinol, lariciresinol, isolariciresinol and demethoxy secoisolariciresinol were also found in flaxseed (Meagher et al., 1999;Sicilia et al., 2003). Lignans, which are a subgroup of isoflavonoids, exist in nature in two forms: plant and mammalian lignans. Lignans found in flaxseed have a structure similar to the estrogen hormone in the body. Lignans in flaxseed are in the group of plant-derived lignans (Webb and McCullough., 2005).

Products such as the seeds of the flax plant, the pulp and flour obtained from the seeds, which contain lignans of plant origin, are very rich sources of lignan content. Plants containing oilseeds such as sesame and sunflower seeds, grains and their bran contain less lignans than flaxseed compared to fruits and vegetables (Table 1)(Meagher and Beecher, 2000).

Table 1. Lignan contents of some plant foods rich in lignans (Meagher and Beecher, 2000)

Food Source	Lignan amount (µg /100 g)	Food Source	Lignan amount (µg /100 g)
Flaxseed	370 000	Carrot	478
Sesame Seed	2900	Garlic	382.6
Sunflower seeds	609.5	Onion	91.0
Wheat	8.1	Green pepper	124.0
Wheat Bran	110.1	Potatoes	16.0
Barley	58	Tomatoes	58.1
Oat	13.7	Blueberry	1510
Oat Bran	178.8	Strawberry	1578
Rice	112-232	Orange	74.6
Cabbage family	185-2321	Black Tea	2787
Broccoli	437.3	Green tea	2646
Red Beetroot	99.5	Coffee (instant)	716

Flaxseed contains matairesinol, secoisolarikiresinol (SECO), isolarikiresinol, pinoresinol and larikiresinol lignans. The glycoside form of secoisolarikiresinol lignan, the most important lignan contained in flaxseed, is secoisolarikiresinol diglycoside (SDG), the lignan compound, which is formed by binding 3-hydroxy-3-methyl glutaric acid to oligomers with ester bonds (Figure 4) (Struijs et al., 2007; Milder, 2007).

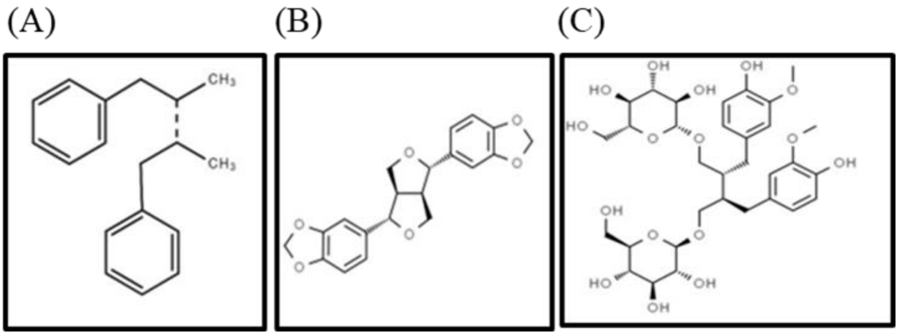

Figure 4. A) Structure of lignans consisting of two phenylpropanoid molecules bonded together B) sesamin, a furanofuran lignin C) Secoisolariciresinol diglucoside, a dibenzylbutane lignan (Meagher et al., 1999; Sicilia et al., 2003).

5. OMEGA FATTY ACIDS IN FLAX SEEDS

Omega-3 fatty acids, which constitute 54-57% of the total oil composition of flaxseed, are an important source of the omega-3 fatty acid α-linolenic acid (ALA), which constitutes 54-57% of the total oil composition (Edel et al., 2015).). Omega-3 fatty acid α-linolenic acid (ALA) and omega-6 fatty acid linoleic acid (LA) are considered essential fatty acids because they are required for health (Figure 5) (Burr and Burr, 1930). The reason why these fatty acids are called essential is that they are needed by the body because they cannot be synthesized by the body. The human body lacks the enzymes necessary to synthesize these fatty acids. Therefore, essential fatty acids must be taken through diet (De Lorgeril et al ., 2001).

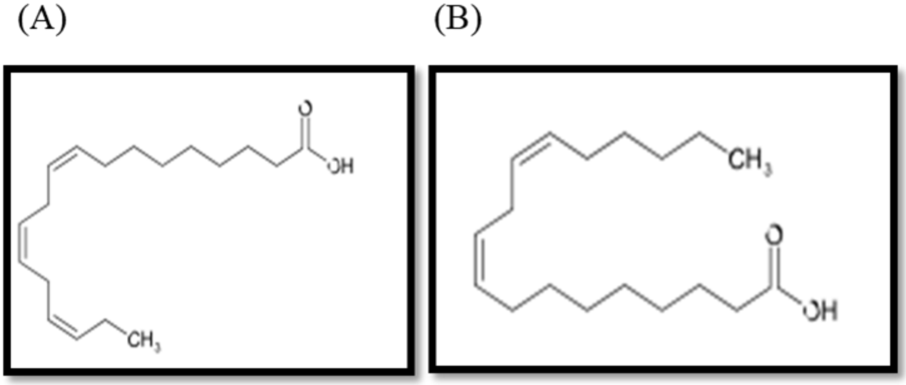

Figure 5. Chemical structures of the two main fatty acids in flaxseed, A) alpha-linolenic acid [ALA], C18:3n-3, and B) linoleic acid [LA], C18:2n-6.

6. HEALTH EFFECTS OF FLAXSEED, LIGNANS AND OMEGA FATTY ACIDS

Epidemiological studies on flaxseed suggest that diets rich in phytoestrogens may reduce the risk of various hormone-related cancers, osteoporosis, and heart disease (Touré and Xueming, 2010; Bartkiene et al., 2015).While flaxseed and its oil slow down tumor development in the early stages of cancer, mammalian lignins have a strong inhibitory effect on cancer formation and stop the progression of new tumors (Orcheson et al., 1998).

It has been shown that the composition of fatty acids in tumors increases the α-linolenic acid ratio and this increase suppresses the growth of tumor cells (Gabor and Abraham, 1986; Gonzalez et al., 1991). Flaxseed contains antioxidant properties. Flaxseed has liver-protective properties.

Multiple studies on flaxseed have shown that flaxseed consumption reduces cholesterol levels (Ridges et al., 2001; Bhathena et al., 2003)

The best-known biological activities of flaxseed are attributed to α-linolenic acids, lignans and, to a lesser extent, soluble polysaccharides (gums). Flaxseed is the most common source of these components (Kapoor, 2005). Scientific studies support that its high omega-3 content, omega-6 rich oil, α-linolenic acid, lignans, high quality proteins and fiber content are biologically active compounds for the prevention of some chronic diseases such as many cancers, diabetes, vascular stroke and cardiovascular disorders (Bernacchia et al., 2014).

Secoisolariciresinol diglycoside (SDG) lignans found in flaxseed are known to have anti-cancer and anti-oxidant properties, as well as anti-viral, anti-bacterial and anti-fungal properties. It is a substance that strengthens the immune system against many different diseases due to its strong antioxidant effect (Collins et al., 2003; Bloedon and Szapary, 2004).

Secoisolariciresinol diglycoside (SDG), enterolactone and enterodiol are the major source of mammalian lignans. It is known that flaxseed is the richest source of mammalian lignans (Nesbitt et al ., 1999; Kamal-eldin et al ., 2001; Degenhardt et al ., 2002) and of secoisolariciresinol diglucoside (SDG), the mammalian lignan precursor of flaxseed (Mazza, 1998). Lignans in flax seeds are generally effective in preventing hormone-sensitive cancer types due to their antioxidant properties (Schweigerer et al., 1992; Prasad, 1997). Studies have shown that secoisolariciresinol diglycoside (SDG), known as the most important lignan of flax, has the ability to scavenge hydroxyl free radicals and has strong antioxidant properties (Touré and Xueming., 2010; Singh et al., 2011). Lignans, enterodiol and enterolactone, are thought to be effective in inhibiting the growth of prostate cancer in humans (Westcott and Muir, 2003).

After being taken orally, plant lignans are converted into mammalian lignans enterolactone (ENL) and enterodiol (END) by microflora (bacteria) in the large intestine in the digestive system (Madhusudhan et al., 2000; Degenhardt et al., 2002; Hu et al., 2007). After hydrolysis of secoisolariciresinol diglycoside, pinoresinol, syringarezinol and lariciresinol, both END and ENL are metabolized to mammalian lignans, while matairezinol is converted to ENL (Heinonen et al., 2001). The production of mammalian lignans depends on both the presence of active flora in the gut and the dietary intake of an appropriate lignan source (Kilkkinen et al., 2001).

The structure of lignans in flaxseed generally contains 34-38% Secoisolariciresinol diglycoside, 15-21% cinnamic acid glycoside and 9.6-11.0% hydroxymethylglutaric acid, respectively. Secoisolariciresinol diglycoside is an antioxidant. Hydroxymethylglutaric acid has hypolipidemic activity and cinnamic acid has antioxidant properties. Therefore, lignans are suggested to have antioxidant and hypolipidemic components (Kamal-eldin et al., 2001; Prasad et al., 2003).

Lignans keep hormone levels balanced by having a phytoestrogen effect in the body. Flaxseed may be beneficial for women, especially during menopause. Flaxseed can alleviate the effects of menopause, such as mood swings and hot flashes. Additionally, it can also balance menstrual irregularities in women caused by hormonal imbalance (Prasad and Chandra, 2003). The main cause of postmenopausal osteoporosis is estrogen deficiency. It is thought that administration of estrogen-like compounds such as lignans and isoflavones may prevent osteoporosis (Coşkun, 2005).

Lignans are said to have protective effects against hormone-related cancers such as breast cancer and non-hormonal cancers such as colon cancer (Rickard and Thompson, 1997; Sung et al., 1998; Chen and Thompson, 2003).

7. CONCLUSION

Flax, its seeds and oil contain many bioactive components that are important for health. Due to the content of flaxseed, it has anti-viral, anti-bacterial and anti-fungal properties. It is known that the lignans, omega-3, omega-6 fatty acids and other components found in the seeds of the flax plant have important health effects due to their high quality protein and fiber content. Studies have shown that flaxseed is beneficial in preventing chronic diseases such as cancer, diabetes, vascular and cardiovascular diseases.

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CHAPTER VI

HEALTH EFFECTS AND USAGE AREAS OF SPICES

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INTRODUCTION

For centuries, humans have utilized medicinal and aromatic plants for their compounds, serving both nutritional purposes and disease treatment. Plants containing alkaloids or glycosides are predominantly used for medicinal purposes, whereas those with essential oils are employed for both imparting flavor and aroma to foods and for their medicinal properties. The aromas of plants containing essential oils are attributed to the phenolic compounds present in their composition. Each plant has a unique chemical composition, and these components impart distinct aromas and flavors to individual plants. Thanks to these characteristics, they enhance food with flavor, scent, taste, and aroma. These compounds sometimes act as appetite stimulants and, at other times, as preservatives due to their antibacterial properties.

Few spice plants are cultivated, as most are sourced through wild harvesting for consumption. Commonly used spices can be found in markets or herbal stores, and with the advancement of industry, they have become easily accessible in packaged forms in supermarkets. Spice consumption is steadily increasing, whether for protection against illnesses, exploring diverse flavors, or preserving food. Changing dietary habits, interest in regional cuisines, and the emergence of new food products have led to the use of different spices and their various forms.

Spices, depending on the plant, can be used either directly or in powdered form. If the raw materials are not to be consumed or marketed immediately, drying and storing them without grinding can prevent aroma loss. However, unground spices may sometimes fail to achieve the desired flavor. Therefore, they should be ground closer to the time of consumption. The finer the spice is ground, the quicker it releases its flavor, but prolonged storage after grinding can lead to significant losses (Akgül, 1993).

Some plants are consumed without drying, while others are cleaned, dried, and then used. In large-scale food production, plants are dried and packaged before being distributed to the market. The need for immediate consumption and storage of fresh products makes drying a necessity. When spices are dried and stored, microbial contamination, spoilage, and volatile oil losses are minimized.

Sterilization of spices before storage holds particular importance. To prevent infestation in spices, methods such as thermal treatment, fumigation, and irradiation can be employed. However, the residues left by the chemicals used in fumigation can pose risks to human health. Additionally, fumigation has limited effectiveness against bacterial spores and insect eggs. It can also lead to deterioration in both the internal and external quality of the crude drugs. Similarly, there are some concerns regarding the potential effects of irradiation on human health. From this perspective, thermal treatment appears to be the most favorable method.

Proper storage conditions are essential to prevent issues such as overheating and the development of bacterial, fungal, or mold-related diseases in stored products. This requires maintaining appropriate humidity and temperature levels within the storage environment, along with ensuring effective ventilation.

Various phytochemicals found in spices are recognized for their therapeutic properties. Phytochemicals are bioactive plant compounds that can act as antioxidants, antimicrobials, antibacterials, and anticancer agents, and they are reported to help prevent cancer, cardiovascular diseases, and inflammatory disorders. Due to these health benefits, spices are considered and used as medicinal plants. The components that give spice plants their characteristic properties vary in type and concentration from plant to plant.

These compounds offer not only nutritional benefits but also exhibit antioxidant, antibacterial, anticancer, anti-inflammatory, analgesic, digestive-supporting, immune-boosting, blood sugar-regulating, calming, anxiety-reducing, and stress-relieving effects. Additionally, it has been identified that these plants may reduce the risk of gastrointestinal cancers by shortening the transit time of food through the digestive system. For these reasons, such plants have been consumed by humans for centuries.

1. SOME SPICE PLANTS AND THEIR USES

1.1. Anise

Family: Apiaceae

Genus: *Pimpinella* spp.

Species: *Pimpinella anisum*

The genus *Pimpinella* L. comprises approximately 200 species, 23 of which are found in Türkiye. Anise, an annual herbaceous plant, is used as a fruit drug. Its fruits are schizocarps, dividing into two mericarps. The color of the fruits ranges from dark green to light brown. The essential oil content in the fruits varies between 1.5% and 3%. The essential oil primarily contains trans-anethole and cis-anethole as its main components. Additionally, it includes compounds such as linalool, estragole, α-terpineol, anisaldehyde, methyl chavicol, and pseudoisoeugenyl 2-methylbutyrate. The oil obtained through distillation is colorless or slightly yellow. At 15°C, anise oil crystallizes and solidifies, and it is soluble in alcohol. (Er and Yıldız 1997; Soltanbeigi and Özliman, 2023). Anise seeds are a rich source of several essential B-complex vitamins, including pyridoxine, niacin, riboflavin, and thiamine. They are also an important source of minerals such as calcium, copper, potassium, iron, manganese, magnesium, and zinc (Shahrajabian et al., 2019; Sun et al., 2019).

1.1.1. Areas of Use

In addition to its use in the production of pastries, bread, dairy desserts, and confectionery, anise is also utilized in soups, meat products, and tobacco manufacturing. Its essential oil is widely used in perfumes, lotions, soaps, cough syrups, chewing gum, and oral hygiene products. In the food industry, it functions as an antioxidant and preservative (Singletary, 2016a). Furthermore, anise is distilled with ethanol to produce unique traditional alcoholic beverages such as Turkish rakı, Greek ouzo, Arabic arak, French pastis, Russian allash, , German küstennebel and Italian sambuca. (Rocha and Fernandes, 2016). It is used in medicinal teas for relieving coughs and as a flavoring agent in lozenges.

1.1.2. Medical Properties

Anise is a medicinal plant used not only in the pharmaceutical industry but also in traditional medicine and folk remedies. Its medicinal use dates back to ancient Egypt. In traditional medicine, it has been employed as a diuretic, carminative, antiseptic, and for relieving migraine pain. Ethnobotanical studies also highlight its use as a remedy for epilepsy, depression, nightmares, and seizures (Soussi et al., 2023).

Recent studies have demonstrated that anise seeds and their essential oil possess antioxidant, antibacterial, antifungal, anticonvulsant, anti-inflammatory, analgesic, gastroprotective, antidiabetic, and antiviral activities. Other significant benefits of anise seeds include their use as a stimulant, carminative, expectorant, insecticidal, vermifuge, digestive aid, antispasmodic, anti-rheumatic, antiseptic, antiepileptic, and antihysteric agent. Many of these medicinal properties have been recognized and utilized since ancient times (Er and Yıldız, 1997; Haşimi et al., 2014; Baydar, 2020). Today, anise is primarily used for its digestive properties and hormonal activities, such as enhancing milk production in breastfeeding mothers (Abouelela et al., 2023). Anise is often confused with another species called *Illicium verum* Hook., commonly known as star anise, as both contain trans-anethole in the composition of their essential oils. However, anise is an annual herb, whereas star anise is an evergreen tree.

1.2. Safflower

Family: Asteraceae

Genus: *Carthamus* spp.

Species: *Carthamus tinctorius*

Safflower (*Carthamus tinctorius*) is an annual plant that is commercially cultivated in countries such as India, the United States, Mexico, Ethiopia, Kazakhstan, Australia, Argentina, Uzbekistan, China, and the Russian Federation. It is also grown to a lesser extent in Pakistan, Spain, Türkiye, Canada, Iran, and Israel. Safflower is valued for its high-quality oil, rich in polyunsaturated fatty acids (linoleic acid), and for carthamin, the orange-red dye derived from its brightly colored flowers

(Gomashe et al., 2021). Every part of the plant has applications in both food and herbal medicine. Carthamin, which is lipid-soluble, is used as a dye in various industries and can produce different colors when treated with different mordants. Safflower seeds contain 13–46% oil, with about 90% comprising two main unsaturated fatty acids: oleic acid (18:1) and linoleic acid (18:2). Standard safflower oil typically contains approximately 6–8% palmitic acid, 2–3% stearic acid, 16–20% oleic acid, and 71–75% linoleic acid (Johnson et al., 1999; Nagaraj et al., 2001; Liu et al., 2016; Kobuk et al., 2019).

1.2.1. Areas of Use

Safflower's young leaves are used as a vegetable in curries or meals, and in India, Burma, and Pakistan, they are commonly consumed in salads. Thornless varieties are utilized as cut flowers in regions such as Latin America, Japan, and Western Europe. In China’s Yunnan Province, there is a large factory dedicated to the production of carthamin dyes. These dyes are mixed with French chalk and used in Japanese cosmetics, particularly in the preparation of lipsticks (Smith, 1996; Gomashe et al., 2021). The flowers are also prepared as herbal tea and are sometimes referred to as "false saffron" due to their vibrant color. They are used as a coloring agent in foods, beverages, medicines, cosmetics, and for dyeing fibers. Safflower meal, a by-product of oil extraction, is commonly used as animal feed. The oil extracted from safflower seeds, rich in oleic acid, is heat-resistant and is widely used for frying foods, in salads, and in margarine production. It is also employed in biodiesel production. Additionally, due to its quick-drying properties, safflower oil is utilized in the paint industry (Knowles, 1989; Soltanbeigi and Özliman, 2023).

1.2.2. Medical Properties

Safflower exhibits various therapeutic properties, including its use as an expectorant and cough suppressant. Due to its high linoleic acid content, it also helps reduce atherosclerosis (hardening of the arteries). Moreover, it has significant effects on the central nervous system, reproductive system, gastrointestinal system, and cardiovascular system. It possesses anticoagulant, hypolipidemic, and antioxidant activities. Tea made from its leaves is used to prevent miscarriage and infertility in women (Soltanbeigi and Özliman, 2023). The seeds and the oil extracted from them have a laxative effect and are also used externally to relieve rheumatic pain (Baytop, 2021). Safflower has long been utilized as a traditional herbal medicine in Asian countries. It is included in the Pharmacopoeia of the People's Republic of China as a traditional Chinese medicine, and approximately 80 herbal medicinal products in the Chinese Pharmacopoeia are associated with safflower (Tong et al., 2021).

1.3. Fenugreek

Family: Fabaceae

Genus: Trigonella spp.

Species: *Trigonella foenum-graecum* L.

Fenugreek (*Trigonella foenum-graecum*), an annual herbaceous plant, contains essential oils in its vegetative parts and seeds. Some of the volatile oil components include butanoic acid, isovaleric acid, caproic acid, and eugenol. Fenugreek leaves and seeds are rich in both macro and microelements and minerals, as well as vitamins such as thiamine, riboflavin, niacin, and vitamins C and E. Additionally, it contains phytomenadione, a vitamin K derivative that aids in blood clotting, along with bioactive compounds such as steroids, alkaloids, saponins, polyphenols, and flavonoids (Güzel and Özyazıcı, 2021; Soltanbeigi and Özliman, 2023).

1.3.1. Areas of Use

Both the seeds and vegetative parts of the fenugreek plant are widely used as spices and in food preparations. In Türkiye, fenugreek seeds are ground and mixed with red pepper, cumin, and garlic to create a coating paste for pastırma (a traditional cured meat). This coating not only enhances the flavor of the pastırma but also prevents contact with air, helping to maintain its freshness for an extended period.

Fenugreek is also used as a food stabilizer to enhance the flavor and extend the shelf life of foods, particularly meat products. In North Africa, it is added to wheat for bread-making, while in Switzerland, it is used in cheeses and pickles (Beyzi ve ark., 2010). It is used as a flavoring agent in cheeses, salads, and curry sauces. Additionally, it is known to be utilized as a forage crop for dairy cattle (Gupta et al. 1996; Gökçe and Efe 2016).

1.3.2. Medical Properties

Fenugreek exhibits a wide range of bioactive properties, including antidiabetic, antihyperlipidemic, anti-obesity, anticancer, antioxidant, antibacterial, and antifungal effects. Additionally, it demonstrates nephroprotective, hypolipidemic, hypoglycemic, and hypocholesterolemic activities (Gökçe and Efe, 2016; Soltanbeigi and

Özliman, 2023). It is commonly used for stomach and kidney disorders, constipation, beriberi disease, treatment of boils, and Parkinson's disease. Furthermore, it has contraceptive effects and is utilized to alleviate menopausal symptoms and manage polycystic ovary syndrome (PCOS) (Baytop 1984; Arslan et al., 1989; Soltanbeigi and Özliman, 2023).

1.4. Sumac

Family: Anacardiaceae

Genus: *Rhus* spp.

Species: *Rhus coriaria* L.

Sumac is a perennial, shrub-like plant that has been used as a spice for various purposes since ancient times, particularly in the Mediterranean region and northern Africa. Among the more than 250 members of the Rhus genus, it is the most economically significant species. The plant derives its name from the red color of its widely used spice product (El-Saber Batiha et al., 2022). The parts of sumac used as a spice are its fruits, which are rich in minerals such as calcium, iron, potassium, magnesium, sodium, and zinc. The fruits contain fixed oils and volatile oils. The fixed oils in the fruits include oleic, linoleic, palmitic, stearic, and malic acids, while the volatile oils contain compounds such as β-caryophyllene, cembrene, δ-cadinene, carvacrol, α-terpinene, limonene, α-pinene, α-phellandrene, p-cymene, and α-terpineols (Soltanbeigi and Özliman, 2023).

1.4.1. Areas of Use

Sumac is widely used not only as a spice in food but also in the cosmetic and pharmaceutical industries. Its fruits are ground and used to enhance the flavor of meat dishes and salads. Due to its high tannin content, the leaves and bark are utilized in leather tanning (Ünder and Saltan, 2019). Additionally, the volatile oil content of sumac contains bioactive compounds that significantly contribute to its biological activity. As a result, the applications of sumac are rapidly expanding beyond food, including its use as a nutraceutical, food colorant and preservative, and as an additive in animal feed.

1.4.2. Medical Properties

The recognition of sumac's medicinal value dates back approximately 2,000 years to the writings of the Greek physician Dioscorides in De Materia Medica, where he discussed its "medical issues" and benefits, particularly as a carminative and diuretic (Riddle, 2006). Thanks to its content of tannins, phenolic compounds, flavonoids, terpenoids, steroids, anthocyanins, and volatile oils, sumac exhibits various bioactivities, including anticancer, antimicrobial (antibacterial, antiviral, and antifungal), antimalarial, antioxidant, cardioprotective, anti-inflammatory, anti-ischemic, and hypoglycemic effects. Additionally, it has a kidney stone-reducing effect and is used to treat cracked heels (Setorki et al., 2012; Ünder and Saltan 2019; Soltanbeigi and Özliman 2023; Toprak and İslek, 2023). Sumac has been reported to have effects on dysentery, dermatitis, conjunctivitis, and liver diseases (Ali-Shtayeh et al., 2013).

1.5. Saffron

Family: Iridaceae

Genus: *Crocus* spp.

Species: *Crocus sativus* L.

Saffron is a perennial, bulbous plant, with its stigmas used as the drug part, making it the most expensive spice in the world. Being triploid (3n=24), it does not produce seeds. The most important active compounds in its stigmas are picrocrocin, crocin, and safranal. The stigmas derive their color from carotenoid pigments, their taste from the glycoside picrocrocin, and their aroma from volatile oils (Rezaeieh and Vaziri, 2012; Cardone et al., 2020; Soltanbeigi and Özliman, 2023). Chemically, saffron contains over 150 compounds, including flavonoids, carotenoids, flavonoid glycosides, monoterpenes and monoterpenoid derivatives, monocyclic aromatic hydrocarbons, amino acids, and alkaloids.

1.5.1. Areas of Use

The crocin pigment and aroma in its stigmas make saffron valuable as a spice and also useful in textile dyeing, particularly in carpet making. It is used to add both color and flavor to soups, non-alcoholic beverages, confectionery, jams, meats, poultry, and seafood (Kanakis et al., 2007; Muşlu, 2021). Saffron contains more than 150 bioactive compounds that have been isolated. Due to its unique composition and properties, saffron is utilized in various fields such as the food industry, perfumery, cosmetics, pharmaceuticals, and medicine (Aissa et al., 2023).

1.5.2. Medical Properties

Ibn Sina stated that the aroma of saffron, particularly the scent of its oil, strengthens the respiratory organs (Mohtashami et al., 2021). Crocus species have been used in both traditional and modern medicine for the treatment of inflammatory diseases. In addition to its antioxidant, antispasmodic, antinociceptive, anti-inflammatory, antidiabetic, and anticancer effects, saffron has been noted for its therapeutic potential in treating depression, insomnia, Parkinson's disease, Alzheimer's disease, gastrointestinal disorders, gynecological conditions, colds, insulin resistance, cardiovascular diseases, and macular degeneration (Zhang et al., 2013; Mzabri et al., 2019; (Godugu et al., 2020; Soltanbeigi and Özliman, 2023).

1.6. Fennel

Family: Apiaceae

Genus: *Foeniculum* spp.

Species: *Foeniculum vulgare* Mill.

Fennel is one of the significant annual spice plants commercially cultivated. Although native to the Western Mediterranean regions, it now grows naturally from the Canary Islands to Western Asia. Stems, leaves, and seeds of the plant are all utilized, with the seeds predominantly serving as a spice. The concentration of fennel essential oil components is reported to vary depending on geographical origin, extraction methods, and stages of maturity (Diao et al., 2014). According to ASTA (American Spice Trade Association) standards, fennel fruits should contain 6-9% ash, 10% moisture, and no more than 1% acid-insoluble ash (Şanlı et al., 2008). The seeds contain 2-4% essential oil and 20-25% fixed oil. Fennel essential oil consists of over 30 compounds, including trans-anethole, limonene, d-fenchone, estragole, terpinene, and pinene. Among these, the amounts of trans-anethole and d-fenchone are particularly important in determining quality. The essential oil must contain at least 80.0% trans-anethole (Baydar, 2020).

1.6.1. Areas of Use

Essential oil is present in all parts of the plant. Fennel is a key ingredient in various industrial applications, ranging from food to cosmetics and pharmaceutical products. It is commonly used in sauces, soups, salads, and meat dishes. Additionally, fennel is utilized in soaps, creams, and perfumes, as well as for preventing insect infestation in packaged foods.

1.6.2. Medical Properties

Fennel has been reported to be effective in the treatment of bacterial, viral, and fungal diseases (Noreena et al., 2023). It exhibits a wide range of biological activities (Badgujar et al., 2014). The unique health benefits of fennel are primarily attributed to its antioxidant content.

Fennel possesses carminative, antispasmodic, and stomachic properties. It exhibits antioxidant, anti-inflammatory, antimutagenic, cardiovascular, anticancer, antimicrobial, antispasmodic, and antithrombotic activities (Kooti et al., 2015; Javed et al., 2020). Its leaves have wound-healing properties, while its roots act as a diuretic. Additionally, it has antifungal properties and is used as a natural pesticide (Baytop 1999; Soltanbeigi and Özliman, 2023). Some studies have found that fennel exhibits estrogenic effects, meaning it mimics the actions of estrogen. Anethole, the main component of fennel essential oils, is considered the active estrogenic agent. It is particularly known for its ability to enhance milk secretion, promote menstrual flow, and facilitate childbirth (Divya, 2022).

1.7. Mint

Family: Lamiaceae

Genus: *Mentha* spp.

Species: *Mentha piperita*

Mint is a perennial herbaceous plant with a creeping stem. It refers to the dried, crushed leaves of *Mentha* species, harvested during the flowering period and properly dried and processed (Anonymous, 2022). The primary components of mint essential oil include menthol, carveol, carvone, piperitone, piperitone oxide, menthone/isomenthone, dihydrocarvone, menthyl acetate, linalool, 1,8-cineole, limonene, α-humulene, δ-cadinol, and other minor compounds (Prakash et al., 2016). The key constituents of the essential oils from *Mentha piperita* and *M. arvensis* are menthol and menthone, while carvone is the dominant component in the essential oil of *M. spicata*. The quality of mint essential oil increases with a higher menthol content (Çelik and Ayran, 2020).

1.7.1. Areas of Use

In Türkiye, the cultivation of *Mentha spicata*, a species primarily used as a spice and rich in carvone (40-80%), is common. The dried leaves of *Mentha x piperita* contain 1.5-3.5% essential oil, with the main components being menthol (45-70%) and menthone (8-24%). Mint is added as a spice to soups, salads, fried dishes, and hot meals to enhance flavor and stimulate appetite (Baydar, 2020). It is also used in cosmetics. Its essential oil is widely utilized as a flavoring and fragrance agent in products such as chewing gum, mouthwash, shampoo, soap, lotion, perfume, cream, cigarettes, toothpaste, and medicines (Rita and Animesh, 2011). Additionally, various studies conducted in many countries have explored the use of mint and its components as potential alternatives to insecticides, yielding positive results (Çelik Biçer et al., 2023).

1.7.2. Medical Properties

Mint exhibits stomachic, cold-relieving, carminative, antipyretic, diuretic, and antiseptic properties. It has a cell-strengthening effect and helps reduce rheumatism and muscle pain. Additionally, it demonstrates antispasmodic, antioxidant, antiseptic, anticancer, antiviral, antibacterial, antifungal, antidiabetic, and insect-repellent effects. Mint is also effective against headaches, supports cardiovascular health, and possesses antivenom properties, making it beneficial for bites from insects and venomous animals (Fleisher and Fleisher, 1991; Loolaie, et al., 2017; Jeong et al., 2018; Soltanbeigi and Özliman, 2023).

1.8. Coriander

Family: Apiaceae

Genus: *Coriandrum*

Species: *Coriandrum sativum* L.

Coriander, a member of the Umbelliferae family and native to the Eastern Mediterranean region, is an annual herbaceous plant widely cultivated worldwide for its leaves, fruits, and essential oil production. It is also one of the significant spice products. The leaves and fruits of the plant are used as the drug parts. The fruits contain 0.03–2.6% essential oil. Coriander drugs are rich in both essential oils and fatty acids. The essential oil of coriander contains components such as linalool, γ-terpinene, and α-pinene (Asgarpanah and Kazemivash, 2012; Özyazıcı, 2017). The main component of the essential oil, linalool, varies between

25% and 80% (Rathore et al., 2013). Coriander also contains sterols, monoterpenes, limonene, borneol, citronellol, camphor, geraniol, coriandrin, and β-sitosterol (Chen et al., 2009; Momin et al., 2012). Additionally, its fixed oil, obtained through solvent extraction, is rich in petroselinic acid (C18:1, cis-6), a fatty acid unique to plants in the Umbelliferae family and not commonly found in other oil plants. The petroselinic acid content of coriander ranges between 60% and 70% (Demir, 2006; Uitterhaegen et al., 2016). Coriander seeds are well-regarded as a health-promoting spice and are ranked highly on the list of medicinal spices.

1.8.1. Areas of Use

Coriander is commonly used in food, beverages, chocolate, Indian curries, salads, soups, and stews (Burdock and Carabin, 2009; Laribi et al., 2015).

1.8.2. Medical Properties

Coriander exhibits a wide range of bioactivities, including antibacterial, antifungal, antioxidant, diuretic, antiepileptic, antidiabetic, sedative, anticancer, antimutagenic, antihelminthic, anticonvulsant, antidepressant, anxiolytic, anti-inflammatory, neuroprotective, antihypertensive, and antimicrobial effects (Deniz et al., 2018; Özyazıcı, 2021). Additionally, it demonstrates fungicidal, parasiticidal, and insecticidal properties (Ulutaş Deniz et al., 2018).

1.9. Cumin

Family: Apiaceae

Genus: *Cuminum* spp.

Species: *Cuminum cyminum* L.

It is an annual herbaceous plant, with its fruits being the part used as the drug. These fruits are rich in both essential and fixed oils. The seeds contain 5-7% essential oil and approximately 21% fixed oil (Sowbhagya, 2013). The essential oil includes components such as cuminal, α-methyl-, γ-terpinene, cuminic alcohol, γ-terpinene, and safranal. Additionally, the essential oil contains monoterpene aldehydes responsible for its aroma, such as cumin aldehyde, gamma-terpinen-7-al, and alpha-terpinen-7-al. The fixed oil is composed of fatty acids like petroselinic acid, linoleic acid, and lauric acid (Başer, 2014; Kaya et al. 2022; Soltanbeigi and Özliman, 2023).

1.9.1. Areas of Use

Cumin is a spice used either on its own or as part of a blend with other spices, such as chili and turmeric, to contribute to the distinctive aroma and flavor of "curry." In Türkiye, cumin's primary use is in meat and meat products, including marinades and sauces for meat preparation (Varlı et al., 2020). In European countries like Norway and the Netherlands, cumin is used in certain specialty flavored cheeses, while in Germany and France, it is commonly incorporated into bakery products such as bread and cakes (Polat and Kan, 2006). The essential oil of cumin is widely utilized in the cosmetics industry (Kızıl et al., 2003). The residue left after the extraction of the essential oil can be used as animal feed.

1.9.2. Medical Properties

It is used in wound treatment, for relieving bloating, and in the management of digestive disorders, colic, and diarrhea. Its antiseptic properties aid in healing inflamed wounds. When consumed as a decoction, it has a calming effect on the nerves, and when applied to the face, it enhances skin beauty. Regular consumption provides liver protection and helps correct abnormalities in blood lipid levels and vision disorders. Additionally, it exhibits antimicrobial, antifungal, insecticidal, anti-inflammatory, analgesic, antioxidant, anticancer, antidiabetic, antistress, hypotensive, immunological, and contraceptive effects. It is also effective against Alzheimer's disease, asthma, infertility, and osteoporosis (Baytop 1984; Polat and Kan 2006; Soltanbeigi and Özliman 2023).

1.10. Thyme

Family: Lamiaceae

Genus: *Thymus* spp.

Species: *Thymus vulgaris* L.

Thyme is a perennial, shrub-like medicinal and spice plant. While all above-ground parts of the plant can be used fresh, the leaves are most commonly utilized as drugs and spices. According to ASTA standards, thyme leaves must contain at least 2% essential oil, while the European Pharmacopoeia requires a minimum of 1% essential oil (Tuğlu et al., 2021). Thyme contains monoterpene phenols such as carvacrol, thymol, and p-cymene, as well as other monoterpenes like α-pinene, 1,8-cineole, camphor, linalool, and borneol (Nieto, 2020). The major components of thyme essential oil, thymol, and carvacrol, contribute to its high antioxidant activity. The primary part of the plant used is the leaves, but the flowers are also dried and utilized (Meriçli, 2010; Süzgeç Selçuk and Eyisan, 2012; Üstü and Uğurlu, 2018; Soltanbeigi and Özliman, 2023). According to the amendment made to the Turkish Food Codex

Communiqué, thyme is defined as the mixture of leaves, flowers, and shoot tips from plants belonging to the *Origanum*, *Thymus*, *Coridothymus*, and *Satureja* (Lamiaceae) genera, which have been properly dried and crumbled, with stems removed. Additionally, the communiqué requires that the genus name (*Origanum*, *Thymus*, *Coridothymus*, or *Satureja*) be specified on the label alongside the term "Thyme" (Anonymous, 2022).

1.10.1. Areas of Use

Thyme has been used for centuries as a flavoring agent, spice, and herbal remedy. Due to its distinctive aroma, this spice is often added to baked goods, stews, meats, salads, egg dishes, and marinades for chicken and fish (Singletary, 2016b). It is a key seasoning in various types of pizza and pairs well with foods such as legumes, tomatoes, peppers, zucchini, and potatoes. In French cuisine, thyme is frequently used in dishes prepared with game and poultry (Hasko, 2023). Since ancient times, thyme essential oil has been widely used in folk medicine for its carminative, antispasmodic, digestive, expectorant, and anti-inflammatory properties (Tohidi et al., 2017). The secondary metabolites of thyme exhibit intriguing biological activities. As a result, thyme essential oils are commonly used in hygiene and skincare products such as colognes, toothpastes, mouthwashes, deodorants, shampoos, soaps, shower gels, and hair lotions (Soleimani et al., 2022).

1.10.2. Medical Properties

Thyme is used for its antispasmodic, disinfectant, headache-relieving, expectorant, anthelmintic, anti-nausea, and intestinal infection-treating properties. It is also effective for chronic lung diseases and fungal skin infections. Additionally, thyme exhibits antimicrobial, anti-inflammatory, hypolipidemic, antimutagenic, antithrombotic, and anticancer potential. In folk medicine, thyme is commonly consumed as tea or used as a gargle for upper respiratory tract infections. Its fat-burning properties support weight loss, and its blood-circulating effects benefit heart health. Thyme is widely used for kidney stone expulsion, treating intestinal parasites, eczema, scabies, foot-and-mouth disease, and epilepsy. However, it may cause adverse effects in certain cases, such as miscarriage in pregnant women, palpitations in thyroid patients, nausea, and fatigue (Benli and Yiğit, 2005; Zeybek et al., 2010; Üstü and Uğurlu, 2018; Soltanbeigi and Özliman, 2023).

2. CONCLUSION

Spices have been an important agricultural product in terms of nutrition, primarily because they add flavor, taste and aroma to foods since the beginning of human settlement. The fact that some spice varieties grow in certain regions of the world due to climate and geographical conditions has increased the importance of their international trade. Conducting research to ensure that products that have an important place in our foreign trade are produced in accordance with standards through production and marketing methods will enable the production of higher quality and therefore higher economic value products, and producers will be able to make more profits. It is necessary to support the opportunities to increase the production of products with low production volumes in Turkey but high foreign trade value. In order to maintain sustainability in products collected from nature, informing the villagers who collect these products about the characteristics of the products and the collection times can be beneficial in the foreign trade of the products.

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CHAPTER VII

PLANTS CULTIVATED FOR SPICE PRODUCTION IN TÜRKİYE

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INTRODUCTION

Türkiye is one of the fortunate countries with significant plant diversity, owing to its unique position at the intersection of three floristic regions. Due to this diversity and widespread distribution, the procurement of medicinal and aromatic plants has historically been carried out through wild harvesting, without the need for cultivation. However, with the increasing population, interest in medicinal and aromatic plants has been growing steadily, both for health and nutritional purposes. As demand rises, limited production has led to insufficient supply, accompanied by an increase in prices.

Wild harvesting has several disadvantages;

The essential oil yields of medicinal and aromatic plants can vary not only across different periods but also on a daily basis. During wild collection, plants are often harvested without considering the time of day or the developmental stage of the plant. This lack of attention results in non-uniformity among the collected plants, ultimately leading to a decline in the quality of their essential oils.

Additionally, there are specific guidelines that must be followed during the drying and storage processes of these products. However, individuals involved in wild harvesting often lack professional expertise and fail to adhere to these standards. Medicinal and aromatic plant materials should be dried in the shade, elevated off the ground, rather than under direct sunlight. Failure to follow these practices can result in both internal and external quality deterioration of the plant material.

Proper storage conditions are equally essential. Continuous air circulation is required to remove moisture from the environment, and the temperature must be maintained at appropriate levels. Otherwise, bacterial and fungal infections, including aflatoxins, may develop on the plants. Such contamination poses significant health risks to consumers using these products.

One of the most significant problems is the unsustainable and unregulated harvesting of these plants from the wild using uprooting, which has brought some endemic species to the brink of extinction. This situation has made the cultivation of these plants a necessity.

Initially, humans sustained their nomadic lifestyles through gathering, but later transitioned to settled life by domesticating and cultivating plants. This shift not only allowed them easier access to these plants but also enabled higher yields. Medicinal and aromatic plants contain various compounds in differing proportions, which give them their characteristic properties. In fact, even the same plant species grown in different regions (chemotypes) may exhibit variations in their chemical composition.

This chemical polymorphism in plants is largely attributed to the biotic and abiotic stress conditions they experience. Plants synthesize these chemicals to protect themselves under such stress conditions. These compounds have biological effects, such as antioxidant, antibacterial, and anticancer properties, as well as therapeutic benefits for certain diseases. These unique properties make these plants highly valued by humans.

The unique properties of plants were initially discovered by chance and passed down orally through generations. Over time, the therapeutic effects of plants began to be systematically studied, leading to the discovery of various activities. In periods when modern medicine was unavailable, people relied on plants for treatment. Even today, traditional medical practices, referred to as 'Folk Medicine,' continue to be utilized.

Civilizations such as the Sumerians, Babylonians, Assyrians, Hittites, Egyptians, Greeks, Romans, Indians, and Chinese conducted studies on medicinal and aromatic plants and practiced folk medicine. The history of medicinal and aromatic plants dates back to ancient times. The earliest written records related to these plants can be traced back to around 4000 BCE. Comprehensive works by the Sumerians and Egyptians followed. During the turn of the millennium, Strabo and, in the first century CE, Dioscorides authored significant works on herbal drugs. With the advent of Islam, further advancements were made, particularly during the 8th and 9th centuries. In the 11th century, Avicenna (Ibn Sina) authored the five-volume work Canon of Medicine. In the 12th and 13th centuries, Ziyaeddin Ibn al-Baytar detailed medicinal and aromatic plants in his book Mufradat Ibn al-Baytar fi al-Tibb. During the 13th and 14th centuries, the Spice Route facilitated the transfer of the East’s wealth of medicines and spices to Europe from India and China (Er and Yıldız, 1997; Baydar, 2020; Soltanbeigi and Özliman, 2023).

1. SPICES

In Arabic, the term 'spices' (baharat) is derived from the plural form of the word bahar, meaning fragrance. Spices are obtained from various parts of plants, including flowers, leaves, seeds, buds, roots, bark, and rhizomes. For a product to be classified as a spice, it must be of plant origin and rich in flavor, aroma, and color compounds. Therefore, medicinal and aromatic plants are also valuable spice products (El-Sayed and Youssef, 2019; Baydar, 2020).

The International Organization for Standardization (ISO) defines spices as any aromatic vegetable product used in cooking to enhance flavor or preserve food (Duru et al., 2019). Spices are mentioned in many sacred texts, both as a source of healing and as a symbol of power. Historical records related to the production, trade, and use of spices have survived from ancient civilizations such as China, India, Persia, Egypt, Mesopotamia, Anatolia, the Hebrews, Greece, and Rome. In Egypt, it is known that various spices, particularly mint, were used in the mummification of corpses as early as 2500 BCE (Şahin Yiğit, 2014).

The first written records regarding the use of spices in food were discovered during excavations in Egypt. Records dating back to 2500 BCE indicate that mustard was used both as a flavoring agent in meals and as a preservative. The trade route where spices, which were of great importance throughout history, were exchanged came to be known as the 'Spice Route.'

For centuries, wars were fought to control the spice trade and this special route. In fact, the Americas were discovered while attempting to alter the route. Spices grown in tropical regions, such as cloves, cinnamon, and black pepper, were among the first spices to spread globally through trade and held significant importance in commerce. Since its inception, the center of the spice trade has been the Middle East. In this region, spices, along with other exotic goods, have been a primary source of income for its nations (Başoğlu, 1982; Hasko, 2023).

Spices are referred to as medicinal and aromatic plants within the category of aromatic plants in some literature, while in other sources, they are directly identified as spices. In addition to enhancing the flavor of food, spices have been used for centuries as food preservatives and for their health-improving properties.

Spices are functional foods; they can demonstrate beneficial effects on specific target functions in the body beyond basic nutritional needs. Since ancient times, spices have been used medicinally for various purposes (Sachan et al., 2018; Banerjee et al., 2024). Spices and medicinal plants are increasingly recognized as valuable sources of antioxidants beneficial against various diseases (Rao et al., 2014).

Medicinal and aromatic plants contain chemical components that were first utilized by humans for healing purposes as medicines, as flavoring agents for food and beverages, and as mental stimulants for mystical interactions with supernatural deities (Inoue and Craker, 2014).

Although the primary purpose of using spices is to enhance the flavor of food or beverages, the positive effects of spices on human health have been emphasized since ancient times (Hasko, 2023).

A significant portion of medicinal and aromatic plants in Turkey are harvested from the wild and made available for consumption. However, some of these plants, particularly those used in industry, are also cultivated. Thanks to cultural practices and application methods, the quality and yield of cultivated plant materials are generally superior to those collected from the wild.

During the harvesting, drying, and storage of medicinal and aromatic plants, many procedural errors are made. Preventing such issues, ensuring higher quality and yield, and obtaining uniform and accurate plant species require cultivation.

Regulations have been established for medicinal and aromatic plants used in the spice industry to ensure the production and market availability of higher-quality products. In particular, under the Turkish Food Codex Regulation on Food Additives, spices are permitted for use in traditional foods, not only as flavor and aroma enhancers but also as preservatives, despite the prohibition of synthetic additives in such foods (Anonymous, 2013). The preservation effect of spices, which extends the shelf life of foods, is primarily due to their antioxidant and antimicrobial properties (Paksoy, 2016). As awareness of the harmful effects of synthetic additives used for flavoring has grown, interest in and demand for natural spices have been increasing steadily (Üner et al., 2000).

The technical and hygienic rules to be followed during the cultivation, harvesting, preparation, processing, storage, transportation, and marketing of spices are outlined in the Turkish Food Codex Spice Communiqué (Anonymous, 2022).

This communiqué provides information on the characteristics of ground, crushed, and whole spices, as well as spice blends. However, spice mixtures containing components such as starch, flour, or yeast extract (e.g., chicken or meatball seasoning blends) are considered outside the scope of this regulation.

Based on the provided information:

A product obtained by appropriately blending various spices is referred to as a spice mixture. Spices must be dried under suitable conditions, either naturally or through appropriate technological methods, and should be ground using techniques that preserve their unique color, taste, and aroma. During natural drying, spices should not come into contact with the soil. Any spoiled, moldy, moisture-damaged, sprouted, hollow grains, or unwanted foreign materials not part of the plant used to prepare the spice must be removed. For ground spices, at least 90% must pass through sieves with specified mesh sizes, and they must not contain substances such as starch, semolina, or bran. Packaging must comply with the Turkish Food Codex Regulation. Labels should indicate the botanical genus name of the product (e.g., Origanum or Thymus for thyme). Pesticide residues must not exceed the limits specified in the Regulation on Contaminants. The storage and transportation of products must be conducted in accordance with the Turkish Food Codex Regulation. In cases of non-compliance with the communiqué, administrative sanctions will be imposed under Law No. 5996.

2. PRODUCTION OF SPICE PLANTS IN TÜRKİYE

Due to its unique position as a bridge between Anatolia, Asia, and Europe, Türkiye has held a significant role in the trade of herbal medicines and spices for centuries. The Turkish Statistical Institute has provided data on the cultivation areas (hectares) and production quantities (tons) of eight different plants categorized under the spice group in Türkiye (red pepper, anise, cumin, black cumin, fennel, capers, coriander, and thyme) between the years 1988 and 2023. These data are presented in Table 1 and Table 2 (Anonymous, 2024).

Table 1. Cultivation Areas and Production Quantities of Spice Plants in Türkiye (1988–2023)

Year	Red Pepper		Anise		Cumin		Theyme	
	A	B	A	B	A	B	A	B
1988	63 670	20 953	205 000	16 000	890 000	50 000	-	-
1989	86 200	21 303	182 000	8 100	420 000	9 000	-	-
1990	83 610	24 216	164 000	9 500	110 000	5 200	-	-
1991	68 020	20 921	176 170	13 400	88 500	4 400	-	-
1992	60 790	16 136	330 000	25 000	154 000	7 000	-	-
1993	56 400	14 492	368 000	28 000	210 000	9 750	-	-
1994	58 810	14 878	410 000	27 500	186 000	7 500	-	-
1995	57 840	13 887	360 000	25 000	171 600	7 100	-	-
1996	61 520	14 750	350 000	19 000	160 000	7 000	-	-
1997	63 200	14 466	340 000	21 000	174 000	7 500	-	-
1998	61 900	14 333	435 000	25 000	245 000	11 000	-	-
1999	57 730	16 080	410 000	23 000	186 580	7 000	-	-
2000	80 940	21 340	360 000	20 000	135 300	6 900	-	-
2001	90 000	20 000	210 000	11 000	300 000	11 000	-	-
2002	70 000	30 000	220 000	13 000	600 000	50 000	-	-
2003	100 000	40 000	215 000	12 300	300 000	20 000	-	-
2004	71 600	30 000	175 300	11 000	285 400	15 000	52 500	7 000
2005	78 000	45 000	165 000	9 500	258 000	14 300	47 000	6 400
2006	66 960	45 861	126 542	8 479	211 540	11 998	58 853	7 979
2007	71 285	67 213	122 906	8 006	183 269	9 159	60 751	5 350
2008	77 747	60 000	118 799	8 594	183 512	8 879	84 133	10 082
2009	91 372	196 900	119 177	9 472	190 110	14 533	84 957	12 329
2010	104 049	186 272	186 450	13 992	171 242	12 587	85 351	11 190
2011	91 557	162 125	211 542	14 879	200 117	13 193	77 707	10 953
2012	112 677	165 527	194 430	11 023	226 294	13 900	94 283	11 598
2013	112 736	198 636	152 431	10 046	247 045	17 050	89 137	13 658
2014	108 508	186 291	140 506	9 309	224 421	15 570	92 959	11 752
2015	112 887	204 131	138 118	9 050	270 247	16 897	104 863	12 992
2016	122 415	228 531	136 552	9 491	268 849	18 586	121 127	14 724
2017	101 710	179 264	121 833	8 418	267 358	19 175	121 472	14 477
2018	119 865	227 380	124 455	8 664	361 761	24 195	139 061	15 895
2019	119 409	240 656	239 171	17 589	321 889	20 245	157 074	17 965
2020	119 869	256 735	155 317	10 716	212 132	13 926	184 711	23 866
2021	126 580	284 694	110 712	6 936	155 122	8 386	199 573	21 174
2022	121 147	273 846	87 616	5 878	131 100	8 130	218 330	33 849
2023	125 517	287 322	60 244	4 521	164 944	11 480	216 137	30 129

A: sowing /planting area (decare) B: production (tonnes)

Tablo 2. Cultivation Areas and Production Quantities of Spice Plants in Türkiye (2012–2023)

Year	Black Cumin		Fennel		Coriander		Capers	
	A	B	A	B	A	B	A	B
2012	2 299	161	15 775	1 862	11	1	-	-
2013	3 261	352	13 848	1 994	11	1	-	-
2014	1 717	140	15 848	2 289	11	1	15	-
2015	4 681	425	15 512	1 461	150	11	15	-
2016	23 160	2 527	17 503	2 464	503	42	3	-
2017	32 560	3 094	16 525	2 022	410	29	-	-
2018	33 864	3 322	23 400	3 067	405	29	20	2
2019	37 085	3 603	33 859	4 655	155	12	25	3
2020	33 773	3 412	22 204	4 365	2 455	188	32	3
2021	83 915	6 435	13 285	2 503	2 612	253	121	18
2022	108 029	10 089	11 875	2 323	1 571	204	124	17
2023	53 358	5 386	8 154	1 108	1 932	222	121	17

A: sowing/planting area B: production (tonnes)

The production of red pepper, while fluctuations in cultivation area and production quantity were observed between 1988 and 1996, a significant increase has been evident since 2000. The production quantity, which was approximately 20,000 tons in 1988, reached 287,000 tons in 2023, indicating the potential adoption of more efficient production methods.

For anise, the cultivation area decreased significantly from 205,000 decares in 1988 to only 60,000 decares in 2023. Accordingly, production declined from 16.000 tons to 4.500 tons during the same period. Although there was an increase in production between 1992 and 1994, a continuous decline has been observed since 2000. This suggests a decrease in both the cultivation area and demand for anise over the years.

Regarding cumin, a downward trend in cultivation areas and production was noted between 1988 and 1994, followed by a noticeable recovery in the 2000s. Production peaked at 24,000 tons in 2018, but recent years have seen a decline in both cultivation area and production. According to spice statistics, no data on thyme cultivation were available until 2004. Records starting in 2004 indicate a significant increase over time. By 2023, the thyme cultivation area reached 216.000 decares, and production rose to 30.000 tons. Thyme has shown substantial growth in both cultivation area and production in recent years, reflecting increased demand for the plant.

Red pepper and thyme are among the plants in high demand both domestically and for export, leading to significant increases in their cultivation areas and production volumes. In contrast, a notable decline in the cultivation areas and production quantities of anise and cumin has been observed over the years. This suggests that these products are less preferred compared to the past or have lost popularity due to competition from other crops.

Black cumin, widely consumed in Turkey and particularly valued for its oil extracted using pressing methods, has also shown remarkable growth. In 2012, black cumin was cultivated on 2.299 decares, yielding 161 tons. By 2021, these figures had surged to 83,915 decares and 6.435 tons. In 2022, black cumin cultivation reached its peak with 108.029 decares and 10.089 tons of production. However, in 2023, both cultivation area and production decreased to 53.358 decares and 5.386 tons, respectively.

The demand for black cumin has been rising steadily since 2016, driving increased production. Particularly since 2016, there has been a significant surge in cultivation area and production, making it one of the fastest-growing products in demand. The decline in 2023 could be a temporary fluctuation.

A fluctuating trend is observed in fennel cultivation. Initially, fennel cultivation areas and production quantities remained relatively stable. In 2012, fennel was cultivated on 15.775 decares, yielding 1.862 tons. Production peaked in 2019, with 33,859 decares and 4.655 tons recorded. However, by 2023, these figures had declined to 8.154 decares and 1.108 tons, respectively, indicating a downward trend after 2019.

For coriander, only 11 decares were cultivated, producing 1 ton, in 2012. By 2020, these values increased significantly to 2.455 decares and 188 tons. In 2023, while the cultivated area decreased to 1.932 decares, production rose to 222 tons. This indicates that despite reduced cultivation areas, improvements in breeding or agricultural practices have resulted in increased yield efficiency. Compared to other plants, coriander has relatively low cultivation and production levels. Although coriander's cultivation area remains small, it shows clear potential as an export product.

As for caper, it has significantly lower production quantities compared to other plants. In 2018, caper cultivation covered 20 decares with a production of only 2 tons. By 2023, the cultivated area increased to 121 decares, but production reached just 17 tons.

In line with the increasing demand for medicinal and aromatic plants on a global scale, Türkiye is trying to take its place in the market by exporting some plant species. The increasing interest in herbal products in particular encourages Türkiye's exports in this sector and contributes to the gradual increase of the country's market share. In order to increase its competitive power in the world medicinal and aromatic plant market, studies to be carried out to increase product quality and production diversity can help Turkey become more powerful in this sector.

3. CONCLUSION

Initially used to add flavor, taste, and aroma to foods, spices have become significant agricultural products due to their expanding range of applications. The cultivation of certain spice plants in specific regions of the world, dictated by climatic and geographical conditions, along with their spread across continents through geographical explorations and increased usage, has heightened the importance of their international trade and even led to commercial conflicts.

Despite Türkiye's favorable climate, soil, and geographical conditions for cultivating these plants, the country remains far from realizing its full potential. The primary expectations of both domestic and international spice markets are the consistent production of spices within a certain quality and standard framework. However, challenges persist in meeting these expectations. Research and development efforts are essential to increase production that meets the sector's desired standards and qualities.

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CHAPTER VIII

GOLD PLANT: SAFFRON (*Crocus sativus* L.)

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INTRODUCTION

Saffron, the dried stigma of the perennial herb *Crocus sativus* L. (Iridaceae), is one of the most expensive spices in the world. It is primarily cultivated in Iran, China, Spain, Morocco, Italy, Greece, and India (Xing et al., 2021).

One of the most expensive spices in the world, the stigmas of *C. sativus* are commonly known as saffron. The metabolites crocin, picrocrocin, and safranal are responsible for saffron's color, flavor, and aroma, respectively. These characteristics, along with other factors such as low-input cultivation requiring little or no irrigation in some places, the absence of chemical fertilizers, and the absence of chemical weed control, make saffron an attractive organic crop for many farmers and researchers. In fact, saffron is a major source of income for many people in certain countries, especially Iran. Low water requirements, tolerance to extreme temperatures (high and low) and a unique life cycle distinguish saffron from other crops and offer excellent opportunities for exploitation of marginal lands. Vegetative growth and flowering of saffron begins in autumn, coinciding with the harvest or dormancy period of other crops. The shoots turn yellow and dry in spring and go dormant in summer as new underground daughter bulbs develop. Adaptation to hot, dry climates has led to saffron being widely cultivated in arid regions around the world (Shokrpour, 2019).

As a result, saffron cultivation is typically favored in countries with lower labor costs, such as Iran and Azerbaijan. However, saffron is also produced in countries like Greece, Spain, Argentina, and the USA, with global production exceeding 200 tonnes. Additionally, new regions, such as China and Japan, are being introduced to saffron cultivation (Husaini, 2014).

1. TAXONOMY AND PLANT CHARACTERISTICS

Classical botanical studies based on morphological characters suggest that *C. cartwrightianus* may be a close relative of *C. sativus*. *Crocus cartwrightianus* is also used as a source of wild saffron. *C. sativus* and *C. cartwrightianus* are nearly identical morphologically, but the most important difference is size: *C. sativus* flowers are twice the size of *C. sativus* flowers. cartwrightianus (Mzabri et al.,2019).

The saffron plant is classified within the Iridaceae family. This herbaceous perennial typically grows to a height ranging from 10 to 25 cm. The bulb itself is sub-ovoid in shape, exhibits variability in size and form. It possesses a sturdy structure and is enveloped by multiple concentric spathes. Each primary bulb generates one to three sizable daughter bulbs from its apical buds, in addition to several smaller bulbs that arise from lateral buds. Saffron features two distinct types of roots: fibrous and thin roots situated at the base of the mother bulb, and contractile roots that develop at the base of the lateral buds. The leaves, numbering between five and eleven per bud, are narrow, measuring 1.5 to 2.5 mm in width, and are characterized by a dark green hue. They can attain lengths of 20 to 60 cm and display a whitish band on the inner side, along with a rib on the outer side. The flowers of *C. sativus* commence blooming in early autumn, typically around late September. These flowers are purple and consist of six tepals—three internal and three external—that converge into a long tube extending from the upper section of the ovary. Upon blooming, the flowers are safeguarded by membranous bracts that are whitish in color. The pistil features an inferior ovary from which a slender style, measuring 9 to 10 cm in length, protrudes. The style culminates in a single stigma composed of three vibrant red filaments, which exceed the length of the tepals. This particular part of the plant holds significant importance for cultivation. Saffron, the spice, is derived from the flower of the saffron crocus, a member of the Iridaceae family. The flower is distinguished by its three stigmas, which represent the distal ends of the plant's carpels, and the style that connects the stigmas to the remainder of the plant. (Kamalipour and Akhondzadeh , 2011).

C. sativus grows to a height of 20-30 cm and features 5-11 true leaves that are protected by 5–11 non-photosynthetic white leaves known as cataphylls. In October, the plant produces blooms that are striped purple and emit a honey-like fragrance (Moshiri et al.,2014).

The subterranean structures of the plant, referred to as corms or bulbs, serve as the means for propagating new specimens, as *C. sativus* does not reproduce via seeds. A notable characteristic of saffron flowers is their three stigmas, which range from 25 to 30 mm in length and gracefully arch over the petals. Additionally, each flower comprises three yellow stamens, which lack the active compounds and are generally not collected. A single bulb can yield between one and seven flowers. It is believed that the cultivated species emerged as a natural hybrid, chosen for its elongated stigmas and perpetuated through cultivation practices. The flowers of *C. sativus* exhibit a light purple hue, but it is the slender, reddish stigmas that are highly valued both as a spice and as a natural dye. Approximately 36,000 flowers are necessary to produce a mere pound of stigmas. (Gohari et al., 2013).

2. PLANT BIOLOGY

Saffron, characterized by its sub-hysteranthe behavior, is a perennial herb that reaches a height of 25 to 40 centimeters. The primary components of saffron plants include the corms, leaf structure, and floral organs.

a. Flower

The flower typically consists of one or more blooms, potentially numbering up to twelve, featuring a perianth made up of six purple tepals (perigone) that converge at the base into a long, narrow tube (Figure 1). The pistil includes a lower ovary from which a slender style, measuring 9-10 cm in length, extends. Additionally, there are three sterile stamens, each with two-lobed anthers. The style culminates in a single stigma, which is composed of three intensely red filaments, representing the culturally significant part of the plant for humans. Some instances of variations with an increased number of stigmas have been documented; however, these variations do not persist into subsequent years and should thus be regarded as somaclonal variations that are not inherited by future generations.

Figure 1. A view from the saffron flower

Figure 2. Harvesting flowers and collecting stigmas

b. Sheet

The leaves range from five to eleven per bud, exhibiting a narrow structure with a green hue, measuring between 1.5 and 2.5 mm in width. Their length varies from 20 to 60 cm, featuring a whitish band on the inner side and a ribbed texture on the outer side. This anatomical feature enables the leaf to twist along its main axis and to form a tubular structure, which helps to minimize evaporation when necessary.

c. Corms

The corm of saffron is a specialized organ that originates from the stem, characterized by condensed nodes and internodes. These corms typically range from 3 to 5 centimeters in diameter and are enveloped in tunics. Mature saffron corms generally exhibit one to three prominent apical buds that will sprout in the subsequent growing season, in addition to numerous dormant axillary buds. Each axillary bud possesses developmental capabilities comparable to that of the primary apical shoot; however, these buds enter a dormant phase after producing only a limited number of leaves. The abundance of axillary buds within the corm system allows the plant to swiftly recover from injury and adapt its growth to varying environmental conditions. Each mother corm generates one to three sizable daughter corms from the apical buds, while several smaller corms arise from the lateral buds. Additionally, saffron features two distinct types of roots: fibrous roots and slender roots located at the base of the mother corm, along with contractile roots that develop at the base of the lateral buds. The latter roots are thicker and exhibit a tuberous form, facilitating the corm's ability to maintain its position within the soil.

3. REPRODUCTIVE BIOLOGY

a. Sexual Multiplication

Saffron is characterized as both autosterile and allosterile, predominantly displaying male sterility. Consequently, it is incapable of seed production. This sterility is attributed to irregularities in triploid meiosis, which result in various abnormalities during gametophytic development and, as a result, lead to defective pollen production.

Therefore, saffron exhibits sterile self-pollination. Documented instances of seed production are exceedingly rare, having been recorded only once. In an in vitro setting, cross-pollination of the ovary of *C. sativus* with pollen from *C. cartwrightianus* and *C. tomasii*—species that are self-incompatible yet allofertile—successfully produced viable capsules and seeds. Furthermore, *C. hadriaticus* is capable of fertilizing *C. sativus*. In contrast, the use of pollen from *C. sativus* to pollinate other species within the Crocus genus does not result in seed formation.

b. Asexual reproduction

Saffron corms serve as subterranean structures that store nutrients, allowing the species to withstand unfavorable climatic conditions and maintain its viability. The development of a corm occurs in multiple phases: the emergence of apical buds, which remain dormant on the surface of the parent corm, typically begins at the end of August or the beginning of September with the onset of the initial autumn rains. Subsequently, the stored nutrients in the parent corm are utilized for the development of flowers and leaves, while new reserves start to accumulate in the preformed daughter corms. The maturation of these new corms occurs concurrently with the decline of the parent corm. The quantity of shoots produced by each corm is a vital determinant, as it affects both flower yield and the number of corms in subsequent generations. This shoot count can be influenced by the size of the corms and their planting depth. Furthermore, micropropagation techniques that utilize corm tissue explants, lateral or apical buds, leaves, and various floral components have been implemented for the in vitro regeneration of saffron (Mzabri et al., 2021).

4. ACTIVE CONSTITUENTS AND CHEMICAL PROPERTIES

The saffron stigma comprises more than 150 compounds, both volatile and non-volatile, which include primary metabolites such as carbohydrates, minerals, lipids, vitamins, amino acids, and proteins, as well as secondary metabolites like carotenoids, monoterpenes, and flavonoids, particularly anthocyanins. Chemical analyses of dried saffron stigma extracts reveal that carotenoids, notably crocin and crocetin, along with the monoterpene aldehydes picrocrocin and safranal, represent the most significant active secondary metabolites found in saffron (Samarghandian and Borji., 2014).

The fundamental composition of saffron comprises 14–16% water, 11–13% nitrogenous compounds, 12–15% sugars, 41–44% extractable solids, 0.6–0.9% volatile oil, 4–5% fiber, and 4–6% total ash. Saffron is a source of two vital vitamins: riboflavin and thiamine, along with trace amounts of β-carotene. The riboflavin concentration varies between 56 and 138 μg/g, positioning it among the highest levels found in food sources. Thiamine content ranges from 0.7 to 4 μg/g, which aligns with typical values observed in vegetables. Furthermore, the petroleum ether extract derived from the bulbs contains essential fatty acids, such as linoleic and linolenic acids. Identified sterols include campesterol, stigmasterol, and β-sitosterol, in addition to various acids like ursolic, oleanolic, palmitic, palmitoleic, and oleic acids. Crocetin, a member of the extensive carotenoid family of natural dyes, lacks provitamin functionality. Most constituents in this category are hydrocarbons, generally represented by the formula $C_{40}H_{56}$, or their oxygenated derivatives. However, a minor subset of carotenoids contains carboxylic acid groups, which do not fit within the standard chemical structure and definition. Crocetin, the aglycone of crocin, is classified as 8,8-diapo-8,8-carotenoic acid and belongs to this limited group. It features a diterpenic and symmetrical structure characterized by seven double bonds and four methyl groups. Its elemental formula is $C_{20}H_{24}O_4$, with a molecular weight of 328.4 g/mol. Crocetin crystallizes into red needles with a melting point of 285°C and displays a yellow hue in solution. It shows slight solubility in basic aqueous solutions (20 µM at pH 8) but is highly soluble in organic bases like pyridine. When its concentration surpasses solubility limits in aqueous media, a yellow precipitate forms. Crocetin is primarily acknowledged for its antioxidant properties, which are linked to its chemical structure, and it is currently the most extensively studied constituent of saffron due to its status as a metabolite (Christodoulou et al., 2015).

Chemical composition analysis indicates that saffron contains approximately 10% moisture, 12% protein, 5% fat, 5% minerals, 5% crude fiber, and 63% sugars by weight, which encompasses starch, reducing sugars, pentosans, gums, pectins, and dextrins. Additionally, saffron has been found to contain trace amounts of riboflavin and thiamine. The concentrations of these chemical constituents can vary significantly based on the cultivation conditions and the region of origin. Numerous analytical studies have been undertaken to explore the diverse array of potential bioactive compounds found in saffron. The primary bioactive compounds include crocin (a polyene mono- or diglycosyl ester), crocetin (a natural dicarboxylic carotenoid and precursor to crocin), picrocrocin (a monoterpene glycoside that serves as a precursor to safranal and a degradation product of zeaxanthin), and safranal itself.

The sensory attributes of saffron, including its color, taste, and aroma, along with its health benefits, will be elaborated upon further. This is indicative of the high levels of carotenoid pigments present in the stigmas of saffron flowers, which are primarily responsible for the spice's color. Both lipophilic and hydrophilic carotenoids have been identified in saffron. The lipophilic carotenoids, such as lycopene, α- and β-carotene, and zeaxanthin, are present in trace amounts. Among the carotenoids, the hydrophilic crocins make up approximately 6 to 16% of the total dry matter of saffron, depending on the cultivar, cultivation conditions, and processing techniques. Crocin 1 (or α-crocin), a digentiobioside, is the most prevalent crocin, noted for its high solubility due to its sugar components. Typically, dark red crocin dissolves rapidly in water, producing an orange solution. Consequently, crocin is extensively utilized as a natural food coloring agent. In addition to its role as a dye, crocin also acts as an antioxidant, effectively neutralizing free radicals and safeguarding cells and tissues from oxidative damage. The distinctive flavor of saffron is primarily derived from its unique chemical composition (Melnyk etal., 2010).

The synthesis of apocarotenoids in saffron is a bio-oxidative process facilitated by the carotenoid cleavage dioxygenase (CCD) enzyme, which cleaves carotenoids. Numerous studies have shown that the stigmas of *C. sativus* are a significant source of apocarotenoids, particularly crocetin and crocin. These apocarotenoids are crucial for imparting the distinctive saffron color, making them valuable as coloring agents in the food industry. Additionally, saffron contains several fat-soluble carotenoids, including lycopene, phytoene, phytofluene, α-carotene, β-carotene, and zeaxanthin. The glycosylation of crocetin results in the creation of a biologically active hydrophilic carotenoid known as crocin. Among the various forms of crocin, α-crocin is the predominant type found in saffron, constituting approximately 10% of its dry weight. Crocin serves as a cellular antioxidant, effectively reducing lipid peroxidation and preserving membrane integrity (Mir et al.,2024).

The vibrant hue of saffron is primarily due to crocin, an 8,8-diapocarotene-8,8-dioic acid, which is the predominant constituent, comprising 6–16% of the dry weight and possessing the chemical formula $C_{44}H_{64}O_{24}$. Crocin serves as the principal pigment in saffron, representing around 80% of its total compounds; it readily dissolves in water, yielding an orange solution, which contributes to its extensive use as a food coloring agent. Additionally, crocetin, the aglycone of crocin, is a carotenoid identified as 8,8-diapo-8,8-carotenoid acid, with the chemical formula $C_{20}H_{24}O_4$ (Kothari et al., 2021).

Saffron petals, owing to their lower cost and significant production volume relative to the stigma, represent a valuable resource for a range of applications, some of which are explored in this review. Although saffron stamens are rich in protein, ash, soluble sugars, and long-chain unsaturated fatty acids, they exhibit lower levels of polyphenols, flavonoids, and polysaccharides when compared to the tepals. Additionally, they are a source of important microelements and antioxidant compounds. The advantageous properties and uses of saffron (stigma) and its byproducts in fields such as medicine, perfumery, cosmetics, and the food industry have been thoroughly documented in existing literature (Lachguer et al.,2024).

4.1. Saffron-Based Monoterpenoids

The other biologically active secondary phytochemical constituents include monoterpenoids, specifically picrocrocin and safranal. These monoterpenoids are produced through the breakdown of zeaxanthin. Picrocrocin is crucial for imparting flavor and a bitter taste, while safranal significantly enhances the distinctive aroma of saffron. Picrocrocin, a monoterpene glycoside, serves as a precursor to safranal and is a primary component of saffron's essential oil. It is predominantly found in the stigma and petals of *C. sativus*, exhibiting properties that may combat cancer and enhance memory. Additionally, picrocrocin is utilized in the treatment of various conditions, including menstrual disorders, cardiovascular issues, depression, and Alzheimer’s disease. Conversely, safranal is primarily located in the stigma of the *C. sativus* flower and has a direct impact on the central nervous system. It functions as an antidepressant and anticonvulsant, and it is also vital in alleviating withdrawal symptoms.

4.2. Saffron-Based Flavonoids

Flavonoids and their derivatives rank as the second most biologically active secondary phytochemical constituents found in the stigmas of *C. sativus*. Numerous types of flavonoids and their derivatives are distributed across various parts of *C. sativus*, exhibiting significant medicinal and nutraceutical benefits. Notable flavonoids and their derivatives include vitexin, orientin, kaempferol, isoorientin, naringenin, astragalin, dihydrokaempferol, myricetin, quercetin, rhamnetin, and populin. Additionally, saffron-derived compounds such as crocin, safranal, picrocrocin, crocusatin D-I, isophorone, lycopene, and crocetin are recognized for their extensive therapeutic properties.

4.3. Phenolic Acids in Saffron

The chemical examination of saffron has identified several types of hydroxycinnamic acids, including chlorogenic acid, caffeic acid, methylparaben, gallic acid, and pyrogallol. Hydroxybenzoic acids serve as precursors in the biosynthesis of flavonoids and have been detected in various parts of *C. sativus*. Additionally, hydroxycinnamic acids such as h-coumaric acid, p-hydroxybenzoic acid, sinapic acid, and vanillic acid have been found in the petals of saffron. Notably, p-hydroxybenzoic acid and benzoic acids have also been identified in the pollen of *C. sativus*.

4.4. Saffron Phytosterols

There are various types of phytosterols present in the different parts of saffron; however, phytosterols like β-sitosterol and stigmasterol were reported from both stigmas and petals while fucosterol was reported only from the petals of *C. sativus*.

5. SAFFRON USES

5.1. Therapeutic Uses

Due to its specific composition, several studies of saffron have reported a broad spectrum of biological activities. These include: antioxidant, anti-tumor, antianxiety, antiviral, anti-inflammatory, antigenotoxic, anticancer, anti-atherosclerotic, anti-diabetic, hypotensive, hypoglycemic, antihyperlipidemic, antidegenerative, anti-tumor, insulin resistant reducers, anti-convulsant activity, anti-nociceptive, anti-Alzheimer, aphrodisiac, stimulant, anti-poison, livotonic, lactogogue, anticancer, nervine tonic, cardiac tonic, carminative, immune stimulator, diaphoretic, diuretic, sedative, emmenagogue, relaxant, febrifuge, anti-stress, antiulcer, antimutagenic, antigenotoxic, memory, and learning enhancer, anticonvulsant, antidepressant, blood pressure regulator, oxygen boosting of tissues, and bronchodilator. These properties are basically due to apocarotenoids, which are bioactive chemicals and include crocin, crocetin, and safranal. Some studies have indicated that saffron can prevent Alzheimer's disease, heart disease, mild-to-moderate depression, cardiovascular diseases, gastrointestinal disorders, severe headaches, neurodegenerative and psychiatric disorders, premenstrual syndrome, and anxiety. It is also considered effective in improving memory and learning skills. Saffron is used in folk medicine and the Ayurvedic health system as a sedative, expectorant, anti-asthma, emmenagogue, and adaptogenic agent. Additional virtues ascribed to saffron are around the gastro-intestinal and genital system, in particular, the ability to stimulate the stomach, decrease appetite, cure hemorrhoids, prolapse of the anus, restrain intestinal fermentations, and help in the treatment of amenorrhea. Saffron has been recommended for use in the reduction of pain and inflammation. It has also been proposed as an analgesic agent. Moreover, saffron extracts have been used to treat fever, wounds, back pain abscesses, gingivitis, and pain related to the eruption of first teeth in children. It is often used to reduce blood cholesterol levels and thus the severity of atherosclerosis, resulting in a reduced risk of myocardial infarction.

5.2. Cosmetology and Perfumery Uses

Saffron serves not only therapeutic purposes but also finds applications in cosmetics and perfumery. It is noted for its anti-sun properties, functioning as a natural UV absorber that safeguards the skin from harmful rays. As previously mentioned in the context of therapeutic uses, saffron possesses anti-carcinogenic qualities, which may aid in the prevention of skin cancers and depigmentation. Furthermore, it has been proposed that saffron exhibits an anti-rhythmic effect on human skin by diminishing melanin levels. Historically, saffron has been utilized in cosmetics as a natural pigment, proving highly effective in skin lightening. Clinical studies have highlighted saffron's anti-pruritic effects and its significant overall benefits for the skin. Additionally, discussions have addressed saffron's anti-aging properties, its effectiveness in treating blemishes such as acne, and its ability to exfoliate and enhance blood circulation in facial skin.

5.3. Culinary Uses

Culinary applications represent one of the primary uses of saffron. Globally, a significant portion of saffron is employed in cooking for both flavor enhancement and as a coloring agent. Chefs and saffron connoisseurs describe its distinctive flavor, which is attributed to its three main compounds: crocin, picrocrocin, and safranal, which influence the color intensity, flavor potency, and aroma strength, respectively. Saffron is utilized to impart color to a wide array of dishes and beverages across various cultures. In India, it is predominantly featured in dishes such as “Kheer,” “Biryani,” “Kashmiri pulao,” and "Kehwa." In Italy, it is a key ingredient in “Risotto alla Milanese,” while in France, it is used in

“Bouillabaisse,” and in Spain, it is essential for “Paella Valenciana.” Additionally, saffron plays a vital role in numerous pastries and breads, many of which are associated with secular or religious celebrations, including the Gugelhupt cake in Europe, St. Lucia buns in Sweden, and various breads during Christmas in Estonia, as well as sweets on the Greek islands and rice pudding during Iranian Shi'ite and Jewish festivities. In Morocco, saffron is used to flavor tea as an alternative to mint and is also incorporated as a spice in traditional dishes such as “koftas” (meatballs with tomatoes).

5.4. Medical and Pharmaceutical Applications

Saffron is recognized for its numerous medicinal properties. In contemporary times, the increasing and effective utilization of saffron in medical and alternative medicine has garnered significant interest from researchers. In traditional medicine, saffron is attributed with various benefits, including its roles as a relaxant, expectorant, stimulant for digestion, spasmolytic, and its applications in menstruation regulation and abortion. Historically, saffron has been employed to treat conditions such as blood diarrhea, fever, measles, hepatitis, liver and spleen cirrhosis, urinary infections, cholera, diabetes, and skin disorders. The English pharmaceutical codex includes discussions on saffron syrup, glycerin, and tincture. Saffron is known to stimulate appetite and aid digestion, while its essential oil possesses relaxant properties that may be beneficial for insomnia of a nervous nature. Due to its effects on the bronchial system, saffron is utilized in the treatment of chronic bronchitis and other pulmonary diseases. In South Asia, it is commonly used for ailments related to the kidneys, liver, bladder, and cholera treatment. The external application of saffron tincture is effective for skin conditions such as impetigo. The traditional understanding of saffron's medicinal properties has piqued scientific curiosity, leading several research institutions to explore its biological and therapeutic potential over the past decade. Recent findings indicate that crocin and crocetin can lower blood bilirubin levels and reduce cholesterol and triglyceride levels. Furthermore, numerous studies have reported the anticancer and antitumor effects of saffron, suggesting it may serve as an alternative to chemical medications. Some notable medicinal properties of saffron include: **i.** Aids digestion, fortifies the stomach, and acts as an antitympanite. **ii.** Enhances sexual desire. **iii.** Functions as an analgesic, particularly for colicky pain and gingivitis. **iv.** Combats tumors and neutralizes free radicals, thereby countering cancerous cells. **v.** Acts as a euphoriant, alleviates neuralgia, serves as a tranquilizer, improves memory, enhances concentration, and promotes responsiveness (Moghaddasi, 2010).

5.5. Other Uses

Numerous studies have identified various additional potential applications of saffron beyond those previously mentioned. While saffron has historically been utilized as a dye in the textile sector, this practice has largely diminished due to the advent of synthetic coloring agents (Aissa et al., 2022). The stigma of saffron comprises over 150 chemical compounds, with three primary secondary metabolites—crocin (a coloring agent), picrocrocin (a flavoring agent), and safranal (a fragrance agent)—being particularly significant in contributing to saffron's pharmacological properties. In the culinary field, saffron serves as a flavoring agent, while in the pharmaceutical realm, it is employed for its sedative, antispasmodic, analgesic, appetite-stimulating, and stomach-tonic effects (Razavi et al.,2013; Fallahi & Mahmoodi., 2018).

6. CLIMATE AND CULTIVATION

Saffron is cultivated under a variety of environmental conditions with successful results. In Italy, saffron is grown in Navelli, at altitudes Saffron is cultivated successfully across a range of environmental conditions. In Italy, it is primarily grown in Navelli, situated at altitudes between 650 and 1100 meters above sea level, where the average annual rainfall is approximately 700 mm. In Sardinia, saffron is cultivated in San Gavino Monreale, at elevations ranging from 50 to 140 meters, with annual precipitation varying between 300 and 600 mm. In Greece, the cultivation takes place in Kozani, Macedonia, at altitudes of approximately 650 to 700 meters, where the annual rainfall is around 560 mm. In Spain, particularly in the regions of La Mancha and Castile, saffron is grown under conditions with rainfall between 250 and 500 mm, often utilizing irrigation methods (Gresta et al., 2008).

The saffron plant flowers once a year, necessitating a hand-harvest within a limited timeframe. This herbaceous plant is resilient to sunlight and can endure temperatures below 15 °C. It flourishes in clay and calcareous soils with a pH level ranging from 6 to 7. The pistil of the saffron flower features three reddish-orange stigmas that release a distinctive fragrance. Following the handpicking of the flowers, the stigmas are meticulously separated, dried, and processed to yield saffron. (Kajkolah et al., 2024).

Figure 3. Saffron flower harvest

Most crop management practices, such as planting, weeding, flower harvesting, and stigma separation, are performed manually across the globe. This labor-intensive nature renders saffron cultivation both demanding and costly. Saffron can be cultivated as either a perennial or an annual crop, with the duration of cultivation differing by region: up to four years in Spain, up to eight years in Greece and India, and up to twelve years in Morocco. As the crop matures, typically after four to five years, the yield of stigmas and corms generally decreases due to competition for water and essential nutrients, as well as heightened vulnerability to fungal infections caused by overpopulation. Proper soil preparation is vital prior to saffron planting to achieve a loose texture. The soil should be tilled to a depth of approximately 30 cm, followed by cover cropping and leveling to ensure it is devoid of weeds. Constructing raised beds, measuring 1.5 m in width and 15 cm in height, with 30 cm pathways, can aid in maintenance. Saffron flourishes in neutral to slightly alkaline, loose, and well-drained soils. High-quality saffron and optimal yields can be achieved through corm cultivation in controlled environments, such as plastic tunnels, greenhouses, and growth chambers utilizing hydroponic systems. Various studies have refined parameters including nutrient solution composition, fertilizers, corm size, planting density, and substrates such as perlite, vermiculite, and peat moss. Crop rotation is crucial for sustaining soil health, restoring fertility, enhancing soil structure, and managing pests and diseases. The preceding crop should be free from disease, ideally a legume, while avoiding crops like alfalfa, potatoes, and sugar beets that may harbor diseases affecting saffron. The suggested rotation period ranges from three to eight years. Furthermore, saffron can be cultivated in the spaces between rows of almond trees, vines, other fruit trees, or ornamental plants like roses. Saffron is particularly well-suited for arid and semi-arid regions due to its drought resistance and ability to remain dormant (Lachguer et al., 2024).

7. CONCLUSION

Saffron is an expensive spice plant grown in various agricultural lands around the world, predominantly in Iran. It is utilized by food and dye industries worldwide. Numerous researchers have demonstrated its therapeutic properties, indicating its potential as a medicinal crop. Researches confirm that the high economic value of saffron, significant employment generation, the ability to store the product at low cost for extended periods, a short cultivation cycle, limited irrigation requirements, and export opportunities are key reasons that have heightened the interest of both farmers and non-farmers in saffron cultivation.

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CHAPTER IX

THE USE OF PLANTS BELONGING TO THE GENUS LAVANDULA IN THE FIELD OF HEALTH

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INTRODUCTION

Plants of the *Lavandula* genus are a collection of species endemic to the Mediterranean region, characterized by their abundant phytochemical constituents. Species of this genus are cultivated globally for decorative and therapeutic applications. Notable members of this genus in the Lamiaceae family, originating from the Mediterranean, include fine lavender (*Lavandula angustifolia Miller*) and the natural hybrid lavandin (*Lavandula x intermedia Emeric ex Loisel*) (Salehi et al., 2018). Since the early twentieth century, *Lavandula* species have been commercially farmed for the extraction of their essential oils (EOs) and absolute extracts using solvent extraction. These essential oils are extensively utilized in the fragrance and cosmetics sector, food processing, and aromatherapy. Lavender (*L.angustifolia, L. officinalis, L.vera*), referred to as "therapeutic lavender," "true lavender," and "common lavender," is an evergreen perennial species. Its name originates from the Latin terms "lavo" and "lavare," signifying "to wash" or "to cleanse" (Batiha et al., 2023). English lavender (*L. angustifolia*) is the most commonly preferred lavender species, although other species such as *L.burnamii, L. dentata, L. dhofarensis, L. latifolia and L. stoechas* are also used (Basch et al.,2004).

The *Lavandula* genus consists of 39 species, as well as numerous hybrids and approximately 400 registered cultivars (Benabdelkader et al., 2011). These plants appear as annual or herbaceous plants and small shrubs with aromatic leaves and flowers that vary in terms of their morphological characteristics, habitats and chemical compositions (Lesage-Meessen et al., 2015). Lavender species, native to the Mediterranean region, have spread and are cultivated mainly in Europe, the Canary Islands, Madeira, North Africa, Southwest Asia, the Arabian Peninsula, India and North and South America (Benabdelkader et al., 2011). The foremost countries in lavender essential oil production include Bulgaria, France, China, Ukraine, Spain, and Morocco (Lesage-Meessen et al., 2015). Lavender has a longstanding history of therapeutic application. (Lesage-Meessen et al., 2015). Lavender exhibits anti-inflammatory (Algieri et al., 2016; Shaikh et al., 2014; Sosa et al., 2005) sedative (Linck et al., 2009) antidepressant (Kageyama et al., 2012), antispasmodic, anticholinesterase (Costa et al., 2013), antifungal (Zuzarte et al., 2013) and antibacterial properties (Turgut et al., 2016). Lavender is a well-known medicinal plant for internal use to relieve symptoms of mental stress, insomnia and digestive problems, as well as for external use in aromatherapy, to treat neuralgia and as an antiseptic (Dobros et at., 2022).

The genus *Lavandula* belongs to the family *Lamiaceae* and is naturally found in a wide area from the North Atlantic to the Middle East, especially in the Mediterranean basin. The family *Lamiaceae* is characterized by plants with opposite, cross-leaved, and quadrangular stems. These plants are herbaceous, biennial species that grow in dry, sunny, calcareous (fine lavender and lavender jelly species) or siliceous (lavender stoechas) soils. The family *Lamiaceae* is divided into a total of seven subfamilies, including the subfamily *Nepetoideae*, which contains the lavender species. The taxonomy of the genus *Lavandula* has been extensively described, especially by Upson and Andrews, and includes more than 39 species, 79 intraspecific taxa, and hybrid species. The genus is classified into three subgenera (*Fabricia, Sabaudia, and Lavandula*) and eight sections. The main species cultivated are fine lavender (*L. angustifolia*), lavender jelly (*L. latifolia*), woolly lavender (*L. lanata*), and lavandin (*L.* × *intermedia*, a sterile hybrid of *L. angustifolia* and *L. latifolia*). All of these species are classified in the genus *Lavandula* and subgenus *Lavandula*. The genus *Lavandula* also contains many subspecies and hundreds of cultivars (Guitton et al., 2010; Moja et al., 2016; Passalacqua et al., 2017).

Plants belonging to the *Lavandula* genus are perennial shrubs, usually semi-shrubs, and can sometimes grow up to one meter tall. The flowering period lasts from mid-June to mid-July, and they prefer acidic soils. Lavender can grow in compact clusters, reaching about 40-60 cm in height. The stem of the plant is green at the top and woody at the bottom. The leaves are lance-shaped with curved edges and have a fibrous root system. The silvery-green leaves are covered with a layer called tomentum, which protects them from wind, intense sunlight, and excessive water loss. The flowers of lavender are pale purple and arranged in circular clusters, with 3-5 flowers in each cluster. Additionally, white-flowered (Alba and Nana Alba) and pink-flowered (*Rosea*) lavender varieties are also grown. (Mhmood et al., 2020). Inflorescences are common in the genus *Lavandula*. The flowers, borne on pedicels, are arranged in whorls and are held in cylindrical or quadrangular panicles (Mohd et al., 2016).

1. THE HISTORICAL USE OF LAVENDER

Lavender has been a significant plant utilized for therapeutic and cosmetic applications since antiquity. The ancient Egyptians employed lavender in the processes of mummification and cosmetic applications. Ointment jars resembling lavender were discovered in Tutankhamun's tomb, believed to provide soothing and therapeutic properties. Furthermore, lavender was utilized as a medicinal substance exclusively by the royal family and the high priests (Kadam et al., 2023).

During the Roman era, lavender served as a fragrant agent in public baths, particularly in those used by the affluent elite. Moreover, lavender oil was regarded as an efficacious remedy for skin treatment, massage, and repelling insects such as mosquitoes and fleas. Dried lavender sachets were utilized in bedding to deter insects (Biesalski and Prakash, 2015).

Lavender was introduced to England by the Romans and utilized by military troops for therapeutic purposes. Subsequently, following the removal of the Romans from the region, lavender was neglected for a period. During the Middle Ages, this plant was predominantly cultivated by monks and nuns within monasteries. In 812 AD, the Holy Roman Empire assigned monks the responsibility of cultivating therapeutic plants, with lavender being cultivated at Merton Abbey in England during this era (Boniface and Middleton, 2019).

In the Tudor era, lavender saw a resurgence in popularity and was predominantly cultivated in private gardens. Lavender, utilized in washing rooms, was positioned on items, imparting its pleasant fragrance, which was thereafter absorbed. Queen Elizabeth utilized lavender for treating migraines and was recognized for her fascination with the herb. King Charles VI of France utilized lavender in the upholstery of sofa cushions. In the 17th century, lavender was seen as a safeguard against illnesses, leading to its heightened popularity throughout that period. Lavender was widely regarded as a panacea and was thought to offer protection against the bubonic plague of 1665. In the Victorian era, lavender gained significant popularity among women, and dried lavender blossoms were placed in closets to disseminate its pleasant fragrance. Furthermore, the London district of Mitcham emerged as the hub of lavender oil production during this era (Waring, 2002; Gupta and Sharma, 2017).

Lavender is utilized in Traditional Chinese Medicine (TCM) to address several conditions, including anxiety, infections, and fever. Likewise, Arabic medicine employs lavender for renal issues and abdominal discomfort (Kadam et al., 2023).

2. THE IMPACT OF *LAVANDULA* GENUS ON CANCER-RELATED COMPLICATIONS

Throughout recent progress in cancer diagnosis and treatment, cancer patients continue to have physical and psychological problems associated with this chronic illness, particularly during therapy. Cancer profoundly affects sufferers' mental wellbeing. The prevalence of anxiety and sadness is significantly elevated in patients diagnosed with cancer (Faller and Siedler, 2019). Sleep disturbances are prevalent among these individuals, occurring in 25% to 59% of cases, and can adversely impact health outcomes (Miller and Rosenthal, 2017). Symptoms like pain and exhaustion, commonly experienced by patients receiving cancer therapy, adversely impact the treatment process, cancer recovery, quality of life, and survival rates (Given and Given, 2017). Research on lavender and cancer-related issues indicates that lavender may provide benefits in cancer treatment and in alleviating cancer-related symptoms. Lavender may be very beneficial in alleviating the negative effects of cancer treatment and enhancing the quality of life for cancer patients. The calming and anxiety-reducing properties of lavender may assist in the management of anxiety and depression among cancer patients. Lavender essential oil, specifically, assists in decreasing levels of anxiety in cancer patients when employed in aromatherapy. A study demonstrated that lavender oil decreased anxiety and enhanced overall well-being in cancer patients. Lavender has been utilized to alleviate depressive symptoms in cancer patients. (Hadfield, 2001). Patients utilize lavender throughout cancer treatment to alleviate symptoms including pain, weakness, and exhaustion. Aromatherapy applications, in particular, can be advantageous in alleviating pain and stress. Researchs demonstrates that lavender oil effectively alleviates postoperative pain in cancer patients and promotes relaxation during recovery. The potential of lavender in analgesia and bodily relaxation has also been emphasized in the researchs (Keyhanmehr et al., 2018; Li et al., 2022). Numerous studies indicate that lavender oil enhances sleep quality and is advantageous for cancer patients experiencing insomnia. Lavender essential oil, specifically, can enhance sleep quality. A study shown that lavender oil enhanced sleep patterns and elevated sleep quality in cancer patients (Koulivand et al., 2013). Lavender oil may effectively mitigate chemotherapy adverse effects, including nausea, vomiting, and headaches. Aromatherapy with lavender oil may assist in alleviating these symptoms during chemotherapy. A study indicated that lavender oil alleviated chemotherapy-related adverse effects, including nausea and vomiting (Li et al., 2022). The impact of lavender on mitigating psychological and physical symptoms of cancer indicates its potential utility as an adjunct in cancer therapy and in decreasing treatment-related adverse effects. Nonetheless, further investigation is required to enhance comprehension of these consequences in clinical practice.

3. THE ANTICANCER PROPERTIES OF THE *LAVANDULA* SPECIES

The anticancer potential of *Lavandula* species has garnered interest due to recent research that have elucidated the impact of its biologically active components on numerous cancer types. The anticancer effects of *Lavandula* are primarily mediated through mechanisms including apoptosis induction, antioxidant activity, anti-inflammatory properties, and inhibition of cell proliferation.

The anticancer properties of *Lavandula* species arise from their physiologically active compounds. Among these components, terpenoids (notably linalool, linalyl acetate, borneol, and 1,8-cineole), phenolic compounds (flavonoids, caffeic acid derivatives), and essential oils are prominent. Linalool, the principal constituent of *Lavandula*, induces cell death by exhibiting cytotoxic actions on diverse cancer cell lines. It has been documented to exhibit antiproliferative and apoptotic effects, particularly on breast, lung, and colon cancer cell lines (Hajhashemi, V., and Ghannadi, 2004). The anticancer activity of this compound, which has a chemical structure of 3,7-dimethyl-1,6-octadien-3-ol, is primarily associated with the suppression of cell proliferation, activation of apoptotic signaling pathways, regulation of oxidative stress levels and inhibition of metastatic processes. Linalool, obtained from lavender, plays a role in the regulation of oxidative stress with its free radical scavenging capacity. In cancer cells, an unbalanced increase in reactive oxygen species (ROS) levels causes DNA damage and triggers cellular death mechanisms. Rosmarinic acid, caffeic acid, and other phenolic compounds present in *Lavandula* species decrease oxidative stress and prevent DNA damage due to their potent antioxidant effects. This inhibits the multiplication of cancer cells and facilitates the induction of apoptosis (Cavanaghand Wilkinson, 2002). *Lavandula* extracts have demonstrated the ability to induce apoptotic pathways in cancer cells. Lavender compounds induce cell death by elevating the expression of pro-apoptotic proteins Bax and Caspase-3, while diminishing the levels of the anti-apoptotic protein Bcl-2. This has been validated in vitro in breast, colon, cervical, and leukemia cell lines. *Lavandula angustifolia* extract induced apoptotic cell death in the MCF-7 breast cancer cell line and reduced cancer cell proliferation by stopping the cell cycle in the G1 phase (Niksic et al., 2016; Tayarani-Najaran et al., 2021; Aboalhaija et al., 2022).

Lavender possesses potent antioxidant effects. This effect safeguards DNA against mutagenic harm. Kozics et al. demonstrated that lavender essential oil provides a protective effect against mutagenic DNA damage by elevating the levels of both enzymatic and non-enzymatic antioxidants (GPx-glutathione peroxidase, SOD-superoxide dismutase, GSH-glutathione) in the HepG2 hepatoma cell line in vitro and in rat hepatocytes in vivo (Kozics et al., 2017). The anti-mutagenic capabilities of lavender extracts, attributed to their potent free radical scavenging capacity (Bouyahya et al., 2017), were evidenced by Evandri et al. through a bacterial reverse mutation assay (Evandri et al., 2005). Furthermore, certain research indicate that lavender extracts exhibit cytotoxic characteristics attributed to the monoterpenoid content in specific lavender essential oils, including camphor, linalool, and linalyl acetate. (Prashar et al., 2004; Woronuk et al., 2011; Soulaimani et al., 2019). In particular, volatile components in *L. angustifolia* oil target cancer cells by triggering oxidative stress mechanisms. It prevents uncontrolled cell growth by supporting apoptosis and autophagy mechanisms (Fahmy et al., 2022). Linalool, present in lavender extracts, exhibits antiproliferative actions by inducing apoptosis and enhancing antitumor immunity in SW 620, Hep G2, A-549, and T-47D cell lines (Chang and Shen, 2014). Antitumor efficacy has been demonstrated through the regulation of oxidative stress in the Sarcoma-180 solid neoplastic model (Jana et al., 2014). Linalyl acetate influences melanoma cell development via regulating oxidative stress through the JNK and ERK signaling pathways (Peng et al., 2014).

4. ANTIDIABETIC EFFECTS OF *LAVANDULA* SPECIES

Research, particularly on *L. angustifolia* and *L. stoechas*, substantiates the antidiabetic properties of *Lavandula* species. The antidiabetic efficacy of *Lavandula* species is mediated by many biochemical and physiological processes. Research on *Lavandula* species has demonstrated that this plant exhibits antidiabetic properties through various pathways, including antioxidant activity, glucose metabolism, modulation of enzymes such as α-glucosidase and α-amylase, insulin secretion, pancreatic effects, and anti-inflammatory processes (Elrherabi et al., 2024).

Lavender is a plant abundant in phytochemicals, including polyphenols, flavonoids, and and terpenoids. These chemicals save pancreatic β-cells by diminishing oxidative stress. Oxidative stress significantly contributes to the etiology of diabetes; the potent antioxidant properties of *Lavandula* species can enhance glucose metabolism(Sebai et al., 2013). Research indicates that *Lavandula* extracts lower blood sugar levels in diabetic animal models. *Lavandula* components are believed to lower hepatic glucose production and enhance insulin sensitivity by inhibiting the processes of gluconeogenesis and glycogenolysis (Şahinler et al., 2022). Species of *Lavandula* may regulate postprandial hyperglycemia by blocking carbohydrate hydrolyzing enzymes, including α-glucosidase and α-amylase. This process resembles that of oral antidiabetic medications frequently employed in diabetes management. (Elrherabi et al., 2024). Preclinical studies indicate that *Lavandula* extracts can enhance insulin production from pancreatic β-cells and ameliorate pancreatic tissue damage (Oliaee et al., 2020). This effect is believed to result from antioxidant and anti-inflammatory capabilities. Compounds found in *Lavandula* species can inhibit inflammation by diminishing the synthesis of proinflammatory cytokines and promote metabolic homeostasis (Dobros et al., 2022). Preclinical studies indicate that extracts from *Lavandula* species exhibit hypoglycemic effects and enhance insulin sensitivity in diabetic rat models. Experimental studies utilizing the methanolic extract of *Lavandula stoechas* demonstrated a significant reduction in blood glucose levels (Kulabas et al., 2018). These effects seem to arise from processes that enhance pancreatic β-cell activity and improve the uptake of glucose in peripheral tissues via antioxidant and physiologically active chemicals present in the plant. The scarcity of clinical data regarding the antidiabetic effects of *Lavandula* species complicates the validation of these findings in humans and emphasizes the necessity for further randomized controlled studies. In conclusion, the antidiabetic properties of *Lavandula* genus plants are attributed to a multimodal mechanism of action involving their antioxidant, anti-inflammatory, and enzyme inhibitory capabilities. Lavender is believed to possess potential as a supplementary medicinal agent in diabetes control. Nevertheless, sophisticated randomized controlled trials are required to validate these effects and incorporate them into clinical practice.

5. EFFECTS OF *LAVANDULA* SPECIES ON STRESS, DEPRESSION AND ANXIETY

Essential oils and extracts from *Lavandula* species, particularly *L. angustifolia* (English lavender), are recognized for their stress and anxiety-relieving qualities. The effects are mediated by the neurological and physiological mechanisms of lavender components on the central nervous system. Lavender oil comprises active constituents, chiefly linalool and linalyl acetate. The application of essential oils through aromatherapy or phytotherapy for alleviating anxiety and stress has gained popularity (Wheatley, 2005; Setzer, 2009); yet, preclinical and clinical research remains insufficient. Lavender essential oil has historically been utilized and sanctioned by the European Medicines Agency (EMA) as a herbal remedy for alleviating stress and anxiety. Medications for anxiety and depression, such as benzodiazepines (BZD) and selective serotonin reuptake inhibitors (SSRIs), exert soothing effects through GABAA receptor binding, however may also induce sleepiness and cognitive impairment as adverse effects. Lopez et al. assessed the impact of lavender (Lavandula angustifolia) essential oil on MAO-A, SERT, GABAA, and NMDA receptors to elucidate the molecular foundation of the recognized anxiolytic and depressive effects of *Lavandula*. Research indicated that the primary constituents of lavender had affinity for the glutamate NMDA receptor, whereas lavender and linalool demonstrated the ability to bind to the serotonin transporter (SERT). Nonetheless, lavender and linalool had little affinity for the GABAA-benzodiazepine receptor. This study indicates that lavender may possess pharmacological characteristics through the modulation of the NMDA receptor and SERT (Lopez et al., 2017).

In clinical practice, lavender oil is often utilized through aromatherapy, topical treatments, and occasionally oral formulations. In aromatherapy, lavender oil regulates the stress response by acting on the limbic system, particularly the amygdala. This leads to reduced cortisol levels and enhanced relaxation (Herz, 2009). It may be utilized in two manners. In the diffuser approach, lavender oil is introduced into a diffuser and disseminated into the room's atmosphere. It is particularly efficacious in high-stress scenarios or pre-sleep contexts (Cavanagh and Wilkinson, 2002). The Steam Inhalation method involves adding few drops of lavender oil to hot water and inhaling the steam for physical and mental relaxation. Research indicates that inhalation of lavender oil markedly decreases anxiety and stress levels. In tropical applications, the active constituents of lavender oil, including linalool and linalyl acetate, are quickly absorbed by the dermis and provide a calming influence on the nervous system. In the massage application technique, lavender oil is typically diluted with carrier oils, such as jojoba oil, and utilized as a massage oil. This application alleviates muscle tension and facilitates mental calm. In the bath treatment technique, several drops of lavender oil are incorporated into warm bath water. This treatment alleviates tension in both the neurological system and the muscles. Studies indicate that lavender oil massage alleviates stress symptoms, particularly in persons subjected to high levels of occupational stress (Cavanagh and Wilkinson, 2002). Oral capsules containing lavender oil may be utilized for treatment of stress and anxiety disorders. "Silexan" is one of the most frequently utilized therapeutic formulations. These capsules are typically administered daily, and their efficacy may require several weeks to manifest. In double-blind, placebo-controlled trials, lavender oil capsules have demonstrated efficacy in alleviating anxiety disorders (Kasper et al., 2014).

6. ANTI-INFLAMMATORY PROPERTIES OF *LAVANDULA* SPECIES

Species of Lavandula, particularly *L. angustifolia*, *L. stoechas,* and *L.latifolia*, possess biologically active chemicals that exhibit anti-inflammatory activities. *Lavandula* extracts and essential oils act on inflammation in three ways: Prostaglandin and cytokine suppression, oxidative stress reduction, and inhibition of enzymatic activity. Lavender essential oil might decrease the synthesis of proinflammatory cytokines (e.g., TNF-α, IL-6). These effects are linked to the inhibition of inflammatory mediators, notably prostaglandin E2 (PGE2), which is crucial during the initial phases of inflammation. In vitro studies indicate that lavender oil suppresses macrophage activation and the activity of nuclear factor kappa B (NF-κB), which governs inflammatory reactions (Pandur et al., 2021). Lavender extracts also assist in regulating inflammatory processes by neutralizing free radicals. This action diminishes the contribution of oxidative stress in initiating inflammation.

Antioxidants, including flavonoids and phenolic substances, mitigate the inflammatory response and avert cellular damage (But et al., 2023). Lavender oil can inhibit the activity of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, which are crucial in the inflammatory process. This method may effectively diminish pain and inflammation (Biltekinet al., 2022). Lavender may mitigate the impact of chronic inflammation on the central nervous system. This is especially crucial in mitigating illnesses induced by neuroinflammation (e.g., Alzheimer's disease and multiple sclerosis). Compounds like linalool have demonstrated the ability to mitigate brain inflammation by inhibiting microglial activation. Species of *Lavandula* are extensively utilized in traditional medicine and contemporary phytotherapy for their anti-inflammatory qualities. The impact of these plants on the treatment of inflammation-related disorders is particularly highlighted through the utilization of their essential oils and extracts. The anti-inflammatory characteristics of *Lavandula* species have been extensively researched in the management of dermatological inflammations. *Lavandula angustifolia* essential oil has been documented to decrease proinflammatory cytokines in situations including atopic dermatitis and eczema. Clinical trials have specifically demonstrated that it reduces levels of TNF-α and IL-1β. (Giovanniniet al., 2016; Cardia et al., 2018).

7. ANTIMICROBIAL PROPERTIES OF *LAVANDULA* SPECIES

Among the most important functions of essential oils in plants is to protect the plant against viral and bacterial infections. There are many scientific studies in the literature showing that essential oils obtained from plants exhibit strong in vitro antimicrobial effects (Bakkali et al., 2008). Species of *Lavandula* have historically been utilized in traditional medicine for their antibacterial qualities. Currently, scientific research substantiate these qualities, particularly regarding the efficacy of their essential oils against bacterial, fungal, and viral infections. The antibacterial properties of *Lavandula* oils are ascribed to their principal constituents. Linalool and linalyl acetate have been identified as potent antibacterial agents against foodborne pathogens, including *Escherichia coli* and *Enterobacter cloacae* (Soković et al., 2010). Other EOL compounds, including limonene, α-pinene, and β-pinene, exhibit antibacterial action against many human pathogenic microorganisms (Inouye et al., 2001). *L. angustifolia* essential oil, at a concentration of less than 1%, shown in vitro efficacy against *Staphylococcus aureus* and *Enterococcus faecalis* (Nelson, 1997). *Lavandula officinalis* leaf and stem parts were investigated for antimicrobial activity. Phytochemical screening showed that borneol 1, 8-cineol, camphor, α-cadinol caryophyllene oxide were the most frequently found chemical constituents in leaves and stems. The antimicrobial activity of the extracts against gram positive bacteria, gram negative bacteria and fungi was investigated and high antimicrobial activity was found against *S. epidermidis* and *S. aureus* (Shafaghat et al.,2012). Lavandula multifida has been found to have antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Canidida albicans* (Benbelaïd et al., 2017). A study on Lavandula dentata essential oil revealed that its primary constituents include 1,8-cineole, sabinene, bicylene, hexane-3-ol, 4-methylene-1-(1-methylethyl), myrtenal, and α-pinene. The antimicrobial examination indicated that it had antibacterial efficacy against the bacterial strains studied, with the exception of *Pseudomonas aeruginosa* (Imelouane et akl., 2009). The primary constituents of the essential oils derived from *Lavandula bipinnata* were identified as transcarveol, pulegone, camphor, and menthol, and these essential oils exhibited antibacterial properties against the evaluated bacterial and fungal strains (Hanamanthagouda et al., 2010).

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CHAPTER X

THE ROLE OF MEDICAL PLANTS IN ATHEROSCLEROSIS: EXPLORATION OF THEIR ANTI-ATHEROSCLEROTIC MECHANISMS

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INTRODUCTION

Atherosclerosis is a disease characterized by endothelial dysfunction, vascular inflammation, accumulation of inflammatory cells and cellular debris. This disease creates lesions in the vessels (Douglas and Channon, 2014; Sima et al., 2009). Atherosclerosis is observed in areas where laminar flow is disrupted, especially at bends or branching points in the arteries (Joris et al., 1983; Williams & Tabas, 1995). It is a fatal disease that begins in the early stages of life, progresses slowly, and can remain hidden without symptoms for long periods before progressing to advanced stages (Hong, 2010; McGill et al., 2000). As atherosclerosis progresses, myeloid cells increase the risk of plaque rupture, which can lead to myocardial infarction (MI) and stroke (Dutta et al., 2012; Koltsova et al., 2013; Mattila et al., 1998). Hyperlipidemia and/or hyperglycemia are the basic factors required for the initiation and progression of arterial lesions. Smoking, poor diet, excess weight, inactivity, diabetes, high blood pressure, and excessive alcohol use are other risk factors (Libby et al., 2019; Sima et al., 2009).

The primary regulator of chemicals moving between the blood, surrounding tissues, and the blood vessel network is the endothelium of the vascular system. Concentration gradients determine whether small molecules can pass through this inner vascular layer and enter the tunica intima. But larger molecules and cells can only pass across vesicles and receptors (Egawa et al., 2013). The intimal endothelium becomes activated and loses its capacity to act as a permeability barrier when exposed to harmful stimuli including high blood pressure, high cholesterol, and proinflammatory cytokines (Nguyen et al., 2019). Changes in vascular endothelial permeability and the composition of the underlying extracellular matrix allow low-density lipoprotein (LDL) to interact with subendothelial proteoglycans in the extracellular matrix, leading to entry into and retention in the arterial wall (Tabas et al., 2007). Endothelial dysfunction initiates a disordered transendothelial flow that causes abnormal accumulation of molecules and cells in the intima. This process results in the intimal expansion and local inflammation seen in early atherosclerosis (De Caterina and Libby, 2008).

Cholesterol-containing LDLs that enter and are retained in the arterial wall are biochemically modified (Majesky, 2007). This modification mimics pathogenic or injury-associated molecular patterns, thereby inducing a low-grade inflammatory response that results in activation of endothelial and vascular smooth muscle cells (Falk et al., 2013; Libby, 2008). Leukocyte adhesion molecules like endothelial leukocyte adhesion molecule-1 (E-selectin), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) are expressed more when intimal endothelial cells, which typically do not bind to circulating leukocytes, are activated (Hwang et al., 1997; Ridker et al., 2001). It leads to the accumulation of circulating monocytes, leukocytes, and cellular, extracellular, and lipid material in the subendothelial space or intima. Infiltrating monocytes, endothelial cells, and macrophage colony-stimulating factor differentiate into macrophages and granulocytes differentiate into macrophages in response to macrophage colony-stimulating factor (Chèvre et al., 2014; Tabas et al., 2015). After consuming modified LDL, macrophages develop into lipid-rich foam cells. The basic mechanism of interaction between macrophages and modified LDL is recognition via receptors. Because of this, a lot of foam cells are created, which results in cholesterol buildup and atherosclerosis (Orekhov and Sobenin, 2018; Pryma et al., 2019). The lipids found in foam cells are mostly cholesterol and cholesteryl esters (Khosravi et al., 2018; Orekhov, 2018). Foam cells accumulate within the arterial intima and form a yellow fatty streak, which is the first stage of atherosclerotic plaque development (McGill et al., 2000; Nguyen et al., 2019; Strong et al., 1992; Tertov et al., 1992).

These plaques change from having a fatty streak to growing intimally. A lipid-rich region called the necrotic core is present during this stage. As the cells die, the necrotic core releases its contents, resulting in the formation of lipid-rich structures (Lusis, 2000; McLaren et al., 2011). As atherosclerotic plaque formation increases, necrotic cores increase as a result of macrophage death and impaired efferocytosis. These two occurrences are linked to thrombogenicity, oxidative stress and an inflammatory microenvironment. They also lead to the death of neighboring cells such as vascular smooth muscle cells (Linton et al., 2016). The necrotic core is surrounded by fibers and these fibers form a cap. These fibers stabilize the plaques (Lusis, 2000; McLaren et al., 2011). The atherosclerotic necrotic core, which is made up of vascular smooth muscle cells that have moved to the luminal side of the artery, and the extracellular matrix are separated by this fibrous cap. It also acts as a structural support that prevents the release of prothrombotic material (Chamié et al., 2011; Watson et al., 2018).

Vascular smooth muscle cells experience apoptosis when atherosclerosis develops as a result of oxidative stress, death signaling receptor activation, and survival pathway blockage (Gonzalez and Trigatti, 2017). The buildup of apoptotic cells cannot be stopped by macrophage phagocytic activity. Oxidative stress and chemical mediators of inflammation are released concurrently with the necrotic demise of these cells. This exacerbates inflammation and accelerates nearby cell death (Coornaert et al., 2018). Cell death-induced metalloproteinases weaken the fibrous cap and make plaque more susceptible (García-García et al., 2012; Johnson et al., 2014). When the plaques rupture, the subendothelial space comes into contact with blood and initiates the clotting process to close the wound (Bentzon et al., 2014; Vergallo and Crea, 2020). First, platelets adhere to and activate subendothelial collagen. Then, large numbers of platelets accumulate in that area to initiate wound healing (Yun et al., 2016). Simultaneously, the prothrombotic elements of the nucleus are released. In addition, they come into contact with the clotting factors of the plasma, activating the coagulation cascade, which leads to the production of thrombin (Badimon et al., 2012; Osaki and Ichinose, 2014). Fibrin, together with platelets, forms a stable structure by covering the lesion. This structure is called thrombus (Libby et al., 2010; Mackman et al., 2007). Following the formation of a thrombus, a sequence of events takes place that increases the lesion's fibrousness, stability, and resistance to rupture. The purpose of this reaction is wound healing, but a biochemical cascade is triggered, causing the intima to expand into the lumen, narrowing the lumen and eventually reducing or completely blocking blood flow to vital organs such as the heart and brain. This can lead to a MI or stroke (Benjamin et al., 2017; Epstein et al., 1992; Grainger et al., 1995; Thanvi and Robinson, 2007; Théroux and Fuster, 1998). An embolus is a clot that passes through the circulatory system as a result of thrombus migration in the artery. Local ischemia and infarction result from the embolus's obstruction of blood flow in the distal arteries (Learmonth, 1948).

Statins, which inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase), lipoprotein lipase activator fibrates and niacin are drugs commonly used in the treatment of atherosclerosis (Ali et al., 2021; Song et al., 2019).

Medicinal and aromatic plants are of great importance in the field of medicine (Orekhov, 2013; Orekhov et al., 2015; Orekhov and Ivanova, 2016). The anti-atherosclerotic effects of these plants are: lowering blood lipid levels, preventing monocyte aggregation, anti-inflammatory, anti-oxidative, preventing vascular smooth muscle cell infiltration, proliferation and plaque formation (J. Y. Kim and Shim, 2019). The possible mechanisms of anti-atherosclerotic effects of medicinal and aromatic plants have been investigated *in vitro* and *in vivo* (Kirichenko et al., 2020). Drugs derived from plants have fewer side effects and are therefore of great interest as therapeutic agents in the prevention and treatment of atherosclerosis. The plant parts listed below have several modes of action that help reduce atherosclerosis (Kajal et al., 2016).

1. MEDICINAL PLANTS WITH BLOOD LIPID LOWERING EFFECTS

High blood lipid levels are a major risk factor for atherosclerosis (Erqou et al., 2009; Nordestgaard et al., 2010). Due to high blood lipid levels, LDL leaks into the arteries and begins to cling to the tunica intima. Infiltration and retention of LDL in the arterial wall may promote the development of atherosclerosis by increasing inflammatory responses. Therefore many studies have investigated the lipid-lowering effects of plants (Li et al., 2013; Skålén et al., 2002).

Apium graveolens extract administered to rats was found to significantly reduce atherosclerosis by reducing serum lipid profiles (Mansi et al., 2009). Ethanolic extract of *Passiflora foetida* has been found to significantly reduce blood lipid levels in diabetic rats (Birudu et al., 2015). *Cinnamomum zeylanicum* bark and *Syzygium cumini* seed extracts have been found to reduce cholesterol, triglyceride and LDL levels while increasing high density lipoprotein (HDL) levels (Sharafeldin and Rizvi, 2015). Administration of *Cynanchum wilfordii* extract to rats fed high-cholesterol diets was found to increase HDL levels while decreasing triglyceride and LDL levels (Choi et al., 2012). *Terminalia arjuna* extraction was found to reduce atherosclerotic lesions in the aortas of rabbits fed a high-fat diet. This extract was also found to significantly reduce LDL levels while increasing HDL levels (Subramaniam et al., 2011).

2. MEDICINAL PLANTS WITH INHIBITORY EFFECTS AGAINST MONOCYTE RECRUITMENT AND ACTIVATION

During the development of atherosclerosis, circulating monocytes adhere to the vascular wall in areas where lipid accumulation occurs. It accumulates and migrates into the subendothelial space through the interaction between monocytes and endothelial cells. It has also been reported that E-selectin, which provides this migration, induces the expression of adhesion molecules such as VCAM-1 and ICAM-1 (Cybulsky and Gimbrone, 1991). Monocytes migrating into the endothelial space differentiate and become macrophages. Modified LDL binds to macrophage scavenger receptors and is taken up into the cell, accumulating within macrophage cells after uptake. Accumulation within this cell results in the formation of foam cells. If migration of monocytes into the endothelial space is prevented, the next step will not occur. However, migration can be inhibited by suppressing gene expression of adhesion molecules (Yu et al., 2013).

Salvia miltiorrhiza Bunge (Danshen) is a traditional Chinese herb. Danshenol A is a diterpenoid isolated from Danshen. Increased intracellular adhesion molecules promote local leukocyte accumulation, adhesion, and subsequent migration into the subendothelial space, which is an early step in atherosclerosis. Danshenol A inhibits Tumor Necrosis Factor-Alpha (TNF-α)-induced expression of ICAM-1 via NADPH oxidase 4 (NOX4) in endothelial cells (Zhao et al., 2017) . Ethanol extract of *Prunella vulgaris* has been reported to inhibit the adhesion of human macrophage cells. This extract was also found to reduce ICAM-1, VCAM-1, E-selectin and nitric oxide (NO) production and Nuclear Factor kappa B (NF-κB) activation in TNFα-induced human aortic smooth muscle cells (Park et al., 2013). Saponins from *Panax notoginseng* decreased the expression of TNF-α-induced endothelial adhesion molecules including ICAM-1 and VCAM-1 as well as the adherence of monocytes to the endothelium in mice (Wan et al., 2009).

3. MEDICINAL PLANTS WITH ANTI-INFLAMMATORY EFFECTS

Every stage of atherogenesis involves inflammation. Unusual inflammatory cell activation is occurring in response to vascular wall lipid buildup. Cytokines and other acute phase reactants are elevated in the blood when inflammation develops in the atherosclerotic artery. Specifically, proinflammatory mediators such cytokines, chemokines, and macrophage migratory potential have increased in plasma levels (Croce and Libby, 2007).

Inflammatory response factors including interleukin (IL)-6 and IL-8 trigger the activation of signal transducer and activator of transcription protein 3 (STAT3). Magnolol, isolated from Magnolia officinalis and applied to bovine aortic endothelial cells, was found to suppress IL-6-induced phosphorylation of STAT3 in a concentration-dependent manner. However, Janus kinase 2 (JAK2) activation and basal ERK1/2 phosphorylation were not inhibited by IL-6-induced Janus kinase 1 (JAK1), suggesting that magnolol therapy markedly decreased STAT3 binding to the IL-6 response element area and ICAM-1 expression on the endothelium surface (Chen et al., 2006). The extract of *Prunella vulgaris* has been reported to inhibit the adhesion of macrophage-like acute monocytic leukemia cells (THP-1) to human aortic smooth muscle cells. By inducing TNF-α, it prevented p38 mitogen-activated protein kinase (MAPK) and ERK phosphorylation (Park et al., 2013). *Tripterygium wilfordii*-derived celastrol prevented apo-E-knockout mice fed a high-lipid diet from phosphorylating and degrading IκB. Additionally, it decreased the synthesis of proinflammatory cytokines such TNF-α and IL-6, NO, and inducible nitric oxide synthase (iNOS) (Gu et al., 2013).

4. MEDICINAL PLANTS WITH ANTIOXIDATIVE EFFECTS

It is known that oxidative damage resulting from the accumulation of free radicals causes many diseases. An essential mechanism in the development and progression of endothelial dysfunction and atherosclerosis is oxidative stress, which is brought on by high level of reactive oxygen species and macrophage inflammation (Kattoor et al., 2017). A large body of evidence from studies suggests that LDL oxidation plays an important role in the pathogenesis of atherosclerosis (Zampetaki et al., 2013). Oxidized LDL is the result of free radical damage to LDL. Instead of binding to its receptor, the oxidized LDL produced in this manner attaches itself to scavenger receptors found on smooth muscle cells and macrophages. By stopping the development and advancement of atherosclerosis, strengthening against LDL oxidation may help prevent atherosclerosis (Glass and Witztum, 2001; Leitinger, 2003; Skålén et al., 2002).

Methanol extract of *Emblica officinalis* fruits prevented the formation of atheromatous plaques by inhibiting LDL oxidation in hypercholesterolemic rabbits (Antony et al., 2006). Corilagin and its analog Dgg16 obtained from Phyllanthus Emblica reduced the formation of malondialdehyde (MDA) resulting from lipid peroxidation in treated human endothelial cells. Additionally, it prevented vascular smooth muscle cells stimulated by oxidized LDL from proliferating (Duan et al., 2005). In HUVECs, *Cyclopogon citratus* extract decreased the production of ROS from oxidized LDL, hydrogen peroxide, and D-glucose (Campos et al., 2014). *Scutellariae baicalensis* extract was reported to be effective against the inhibition of LDL oxidation in mouse macrophage cells and thus has anti-atherosclerotic potential (Kim et al., 2015).

5. MEDICINAL PLANTS WITH INHIBITORY EFFECTS AGAINST VASCULAR SMOOTH MUSCLE CELL INFILTRATION, PROLIFERATION AND PLAQUE FORMATION

Vascular smooth muscle cell migration and proliferation, which contribute to the pathophysiology of atherosclerosis, are known to be linked to apoptosis, aging, inflammation, and matrix alterations, among other biological processes. These processes are of great importance in determining therapeutic targets for both preventing and treating atherosclerosis (Kim and Shim, 2019). Vascular smooth muscle cells constitute most of the extracellular matrix of atherosclerotic plaque. Transforming growth factor beta (TGF-β) and related mediators potently increase the production of interstitial collagens and other matrix macromolecules by vascular smooth muscle cells (Amento et al., 1991). The breakdown of interstitial collagen contributes to the thinning of the fibrous cap of the plaque. These enzymes belong to the matrix metalloproteinase (MMP) family (Galis et al., 1994a; Galis et al., 1994b; Mach et al., 1997). Overactivity of MMPs leads to the destruction of the extracellular matrix. Increased levels of MMP-1, MMP-3, and MMP-9 have been identified in rupture-prone areas of rabbit, mouse, and human atherosclerotic plaques. In addition, rupture-prone areas of human atherosclerotic plaques showed increased levels of MMPs 8, 11, 14, and 16 (Dollery and Libby, 2006; Nagase et al., 2006; Newby, 2005).

Hibiscus sabdariffa extract has been found to have hypolipidemic activity in rabbits fed a high cholesterol diet. Additionally, it has been shown to stop the migration of smooth muscle cells, calcification in blood vessels, and the production of foam cells. (Chen et al., 2003). The extract obtained from Nelumbo nucifera leaf induced apoptosis in rabbits fed high cholesterol and was found to affect the JNK and p38 MAPK pathways in vascular smooth muscle cells. Non-cytotoxic doses of this extract were reported to inhibit MMP-2/9 secretion and cell migration by suppressing the G protein pathway. The study's histopathological findings demonstrated that the extract decreased the production of neointima, inhibited the growth of smooth muscle cells, and decreased MMP-2 release in the rabbits' blood arteries (Ho et al., 2010). *Salvia miltiorrhiza* root aqueous extract contains a chemical called protocatechuic aldehyde, which has been shown to prevent recombinant rat platelet derived growth factor subunit B (PDGF-BB) from migrating and proliferating in vascular smooth muscle cells. Additionally, it has been shown to inhibit the phosphatidylinositol-3'-kinase (PI3K/Akt) and MAPK pathways, which control important enzymes involved in migration and proliferation (Moon et al., 2012).

6. CONCLUSION

In summary, medicinal plants present a valuable and natural approach to the prevention and management of atherosclerosis, offering therapeutic benefits through their diverse bioactive compounds. These plants target multiple pathways involved in atherosclerosis progression, such as oxidative stress reduction, inflammation suppression, lipid profile regulation, and endothelial function improvement. Compounds like polyphenols, flavonoids, and saponins have been shown to inhibit LDL oxidation, lower cholesterol levels, and promote vascular health, reducing the risk of plaque formation. Many plants have demonstrated significant anti-atherosclerotic effects in both experimental and clinical studies. While these findings are promising, further research is essential to determine their long-term efficacy, safety, and optimal usage in clinical settings. Ultimately, incorporating medicinal plants into therapeutic strategies may offer an effective, affordable, and sustainable solution for reducing the global burden of atherosclerosis.

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CHAPTER XI

ECZEMA TREATMENT WITH MEDICINAL AND AROMATIC PLANTS

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INTRODUCTION

The skin has been described as the biggest organ in the human body. This essential organ, which covers the whole body, is responsible for defending it from external threats. Our skin has three layers: epidermis, dermis, and hypodermis (subcutaneous tissue). Each layer is responsible for a distinct duty in maintaining the skin's equilibrium. The thickness, colour, texture, and structure of the skin, our biggest organ, can differ from person to person and even race to race. Skin disorders are prevalent all over the world and can have an impact on a person's mental, social, and physical health (Tabassum and Hamdani, 2014).

Eczema (atopic dermatitis or dermatitis) is a recurrent, itchy and chronic infection of the dermis that affects people of all ages and is highly prevalent around the world. It is a terrible condition that causes red, itchy, and dry rashes on the skin. Inflammation symptoms include redness, swelling, itching, heat, and discomfort (Kim et al., 2019). There are multiple forms of eczema, which are mentioned here;

- **Atopic Dermatitis** is a persistent, hereditary skin disorder. It often starts in childhood.
- **Contact Dermatitis** develops when the skin comes into touch with irritating chemicals or allergens.
- **Seborrheic Dermatitis** manifests as dandruff and redness on oily skin.
- **Dyshidrotic Eczema** develops as tiny, itchy patches on the hands and feet.
- **Nummular eczema** involves cylindrical, coin-shaped sores on the skin (Chu et al., 2024).

This disease can be brought on by genetics, immune system issues, diet, gut microbiota alteration, environmental variables, and failure of the epidermal barrier. Aside from these variables, there are several more reasons why eczema illness develops. These are most commonly associated with T lymphocyte activation or as a condition that coexists with asthma, allergic rhinitis, and atopic illness (Boyle et al., 2011). Eczema therapy first focuses on relieving the patient's symptoms by reducing skin inflammation and itching, rather than improving the look (Thestrup-Pedersen, 2002). Eczema is treated using skin emollients, topical and systemic corticosteroids, antibiotics, and immunomodulatory drugs (Leung et al., 2024).

Physical appearance is a very motivating feature for most people and affects social relationships. Skin diseases found in people can make people unsocial and unhappy in terms of appearance (Bodeker et al., 2017). For this reason, people with skin diseases seek treatment methods and resort to various alternative medicine methods in order to improve their physical appearance rather than the physiological disorder. Numerous people prefer medicinal herbs to cure eczema since natural medicines offer several benefits and have fewer adverse effects.

Medicinal and aromatic plants have been frequently preferred for centuries as an easily accessible natural treatment source for the treatment of many diseases and ailments. For the following reasons, individuals use aromatic and medicinal herbs to cure eczema (Dawid-Pać, 2013):

I. **Belief in Naturalness and Avoidance of Chemical Ingredients:** Herbal remedies are regarded as natural substitutes that are believed to be devoid of chemical additions. In order to prevent the negative effects of synthetic medications, some people prefer natural remedies.

II. **Minimal Adverse Effects Innocent and secure:** Medicinal plants are believed to have little adverse effects when administered correctly. Some patients may have immune suppression or skin thinning as a result of long-term usage of drugs like corticosteroids.

III. **Affordable and Easy to Get:** Medicinal herbs are a cost-effective therapy choice, particularly if they are readily available or produced at home.

Regional Access: Herbs that have been used traditionally can be discovered and utilized with ease in some areas.

IV. **Customs and Traditions: Historical Use:** People have been using herbal remedies for millennia, particularly to address long-term ailments like eczema. This choice may be influenced by traditional information acquired from family or the community.

Cultural Affiliation: Natural remedies are seen as having greater legitimacy in some cultures than contemporary medicine.

V. **Holistic Approach to Body Support:** It's well accepted that medicinal herbs help the body overall in addition to relieving symptoms. Herbs that boost immunity or lower stress levels, for instance, could be favored.

Enhancing the Skin Barrier: Natural advantages like skin healing and moisture may be obtained from medicinal herbs.

VI. **Relaxation of the Mind: A Sense of Closeness to Nature:** Some people report feeling closer to nature as a result of using therapeutic herbs. Psychological relief may result from this.

A Sense of Control: People who are in charge of their own treatment process feel more in control and may become more confident.

VII. **Increased Awareness and Scientific Support Research**

Expansion: As there is more scientific proof that some plants may effectively cure eczema, consumers' confidence in these products has grown. For instance, several studies have demonstrated the beneficial effects of oats, tea tree oil, and aloe vera for eczema.

Minimal Risk of Side Effects: Medicinal herbs may be considered as a first choice prior to medicine, particularly for mild to moderate eczema (Yetkin and Yüksel Başak, 2006).

1. MEDICINAL AND AROMATIC PLANTS USED ECZAMA TREATMENT

Medicinal aromatic plants are kinds of plants that are used medicinally or to enhance their fragrant characteristics. They have medicinal properties and are used to prevent illnesses, heal minor ailments, and mitigate the negative effects of chemotherapy medications. They can have pharmacological properties such as antibacterial, anti-inflammatory, analgesic, and sedative. They attain these qualities through secondary metabolites, volatile oils, alkaloids, flavonoids, tannins, and phenolic chemicals, all of which have biological activity. Medicinal aromatic plants have a variety of applications in both contemporary and traditional medicine (Baser and Buchbauer, 2009). Many herbs are used to treat a variety of skin conditions, including eczema, both topically and internally. These herbs can be used to make lotions, teas, compresses, and extracts (Radha and Laxmipriya, 2015). In this chapter, we summarize the literature on major medicinal plants used mostly to treat eczema, including *Aloe vera, Avena sativa, Centella asiatica, Curcuma longa, Matricaria chamomill*a, *Calendula officinalis, Rosmarinus officinalis, Lawsonia inermis, Lavandula angustifolia and Urtica dioica.* The properties and effects of plants are explained respectively.

1.1. *Aloe vera*

Aloe vera, a succulent plant from the *Asphodelaceae* family with the scientific name *Aloe barbadensis miller*, has been utilized medicinally and cosmetically since prehistoric times. The aloe plant thrives in dry conditions. It has thick, meaty leaves with a water-rich gel inside them. Its blooms are yellow or orange and bloom in the summer. It is naturally found in the warm regions of Africa, the Middle East and Asia, but today it is also grown worldwide and in the home environment (Eshun and He, 2004). It has antimicrobial, anti-inflammatory, antioxidant and immune-boosting properties. The *aloe vera* plant includes a variety of physiologically active components. They are:

- **Polysaccharides:** Moisturize and heal the skin.
- **Anthraquinones**: Antimicrobial and anti-inflammatory properties.
- **Vitamins:** A, C, E (for antioxidant properties), and B12.
- **Minerals:** Calcium, magnesium, and zinc.

- **Enzymes:** Help digestion and promote skin rejuvenation (Reynolds and Dweck, 1999).

The primary explanation for why it is used to treat eczema is that it contains moisturizing characteristics, lowers inflammation in the skin, soothes itching, and promotes quick skin regeneration (Khiljee et al., 2011).

1.2. *Avena sativa*

Avena sativa, sometimes known as white oat, is a subspecies of the *Avena* genus in the wheat family. It is an annual plant indigenous to the warm Mediterranean area. It is now grown in a variety of areas. Oat fruit include β-glucan, glutelin, avenin, and flavonoids. Oats are frequently referred to as a "healthy" or "health food," and they are sold as nutritionally sound. Oats are considered a health food due to their well-known cholesterol-lowering properties (Sur et al., 2008). Oat plants has long been used medicinally to assist balance the menstrual cycle, cure dysmenorrhea, and prevent osteoporosis and urinary tract infections. It has long been used as a calming herb to treat itching and discomfort. Oats include avenanthramides, which are potent anti-inflammatory and antioxidant agents (Duke, 2002).

The efficacy of oats on eczema has been the subject of several clinical research, all of which have demonstrated that using oat extracts significantly reduces skin redness, dryness, flaking, itching, and erythema (Nebus et al., 2012).

1.3. *Centella asiatica*

Centella asiatica (Indian flatweed), commonly known as padeleaf, coinwort, or gotu kola, is a highly medicinal plant from the *Apiaceae* family. In various regions of the world, it grows in wetlands and moderate climates. It includes triterpenes, which have antioxidant properties and the capacity to increase collagen formation in bones, cartilage, and tissues (Premila, 2006). A poultice of the leaves is applied to open wounds. Other stated applications include anxiety alleviation, sleeplessness, immunological booster, diarrhea, and gynecological issues. Indian pennywort is well-known in Chinese and Indian medicine for its amazing skin-soothing, eczema-relieving, and wound-healing properties. Because of its high healing action, it has previously been used to treat leprosy (Kartnig, 1988).

1.4. *Curcuma longa*

Turmeric (*Curcuma longa*) is a perennial herbaceous plant with yellow flowers and big leaves that belongs to the *Zingiberaceae* family. Its homeland is South Asia. *Curcuma longa*, known for its yellow hue, is widely used in Asian cuisine and as a dye (Zari and Zari, 2015).

Many experts have studied turmeric, and it has been shown to have numerous health advantages. It promotes healing, particularly in cancer, diabetes, asthma, anemia, and gastrointestinal diseases. It has excellent wound healing properties in dermatology (Satoskar et al., 1986). It achieves these therapeutic benefits through the antioxidant, antiviral, antibacterial, anti-inflammatory, and antiseptic characteristics of its major metabolite, curcumin (Aggarwal et al., 2007). Numerous skin diseases, such as shingles, eczema, chickenpox, scabies, and allergies, are commonly treated with the fresh juice (Chaturvedi, 2009).

It is also frequently preferred by people in the treatment of eczema. Turmeric's major component, curcumin, has anti-inflammatory and antibacterial effects, making it useful for treating eczema-related skin irritation (Aggarwal et al., 2007; Khiljee et al., 2011).

1.5. *Matricaria chamomilla*

A subspecies of the *Matricaria* genus in the *Asteraceae* family, *Matricaria chamomilla (Matricaria recutita*) is an annual plant that is commonly referred to as chamomile, German chamomile, Hungarian chamomile (kamilla), and wild chamomile. It has traditionally been used to treat cardiovascular disease, colds, insomnia, cancer, and gastrointestinal ailments (Tayel and El-Tras, 2009). Matricaria flower has been demonstrated to be effective when used topically to treat skin inflammations and irritations, bacterial skin infections, diaper rash and cradle cap, eczema, wounds, abscesses, frostbite, and insect bites (Weiss and Fintelmann, 2000). The blossoms are used to produce teas, liquid extracts, capsules, and pills. It is administered to the skin as an ointment or lotion.

In vitro, the essential oil of chamomile and its component α-bisabolol demonstrated antifungal and antibacterial properties (Schulz et al., 2004). In a research on eczema sufferers, a cream containing chamomile extract was compared to steroid creams and found to be more effective and safe (Aertgeerts et al., 1985).

1.6. *Calendula officinalis*

Calendula officinalis L. is a species of *Asteraceae* that is commonly referred to as "Calendula" by the general population. It's an annual plant with a herbaceous stalk. *C.officinalis* is not a naturally occurring species; rather, it is planted as a decorative plant in gardens. It has been cultivated in various regions of the world and is generally only reported momentarily, therefore its origin is uncertain (Güven et al., 2022).

Calendula officinalis has been used medicinally for many years to treat digestion issues, menstrual discomfort, and numerous skin conditions. The leaves and flowers of C. officinalis are high in polyphenols, alkaloids, steroids, tannins, and flavonoids. It has been stated that it is used to treat eczema and psoriasis due to its anti-inflammatory and wound healing effects with secondary metabolites (Bashir et al., 2006).

1.7. *Rosmarinus officinalis*

Rosemary, also known by the scientific name *Salvia rosmarinus* and the popular name 'rosemary', is a shrub with fragrant, needle-like leaves and white, pink, blue, purple flowers. It belongs to the sage family *Lamiaceae* (Khiljee et al., 2011*)*.

The essential oil extracted from the plant's leaves includes phenolic chemicals such as rosmarinic acid, carnosol, and carnosic acid, which can demonstrate anti-inflammatory, antibacterial, and antioxidant characteristics through biological activities (Karadağ et al., 2019). The 1,8-cineole in rosemary essential oil contains terpenes, which have been shown to be a powerful anti-inflammatory (Santos and Rao, 2000).

Because of these qualities, it has long been used to treat atopic dermatitis. Rosemary extract has been demonstrated to be particularly efficient against *Staphylococcus aureus*, which causes inflammation in eczema sufferers and hence slows advancement (Jiang et al., 2011).

1.8. *Lawsonia inermis*

Henna (*Lawsonia inermis*) is a flowering plant belonging to the *Lythraceae* family. Henna, a tall shrub or short tree, is hairless and has several branches. Henna refers to the dye made by drying and grinding the leaves of this plant, as well as the temporary forms formed on the body with this material. It has been used since ancient times to color skin, hair, nails, silk, wool, and leather (Singh et al., 2005).

Henna contains antifungal, anti-inflammatory, analgesic, and relaxing effects. In a clinical research, researchers treated eczema patients with a cream made from henna and a variety of herbs and observed an improvement in eczema appearances and symptoms (Nawab et al., 2008).

1.9. *Lavandula angustifolia*

Lavandula angustifolia, frequently referred to as lavender, is a plant species in the *Lamiaceae* family with pleasant smelling and fragrant qualities. It features silvery, hairy leaves and purple-blue blooms that emerge during the summer. Lavender, which grows natively in the Mediterranean basin, is now widely utilized as a decorative, medicinal, and industrial plant (Baser and Buchbauer, 2009). With its complex chemical content, lavender is appealing to both the medicinal and cosmetic areas. It includes linalool, linalyl acetate, cineole, rosmarinic acid, and coumarins, and it has anti-inflammatory and antioxidant properties (Cavanagh and Wilkinson, 2002). Lavender has several beneficial impacts on the neurological system, digestion, sleep habits, and skin. According to reports, it works very well for treating and relieving eczema symptoms.

The metabolites found in lavender and their favorable effects on eczema are detailed below (Cardia et al., 2018).

- **Anti-Inflammatory Attributes:** Lavender oil is very useful for decreasing inflammation in the skin, which can help alleviate the symptoms of inflammatory skin diseases like eczema.
- **Antimicrobial Effects:** Lavender oil has antibacterial properties, which may lower the risk of bacterial illness. Eczema-damaged skin is more susceptible to infection, and lavender can help regulate the problem.
- **Calming and Itchy Reliever:** Lavender's calming aroma and skin-soothing qualities can alleviate irritation and promote skin barrier healing.
- **The ability to repair skin:** Lavender oil has active compounds that help the skin regenerate. This can help to speed up the healing of eczema-affected skin.

1.10. *Urtica dioica*

Nettle, a member of the *Urticaceae* family with well-known medicinal benefits, grows all over the world, particularly in humid and temperate locations. Its green leaves are round, with sawtooth margins. It's a perennial herbaceous plant. When its prickly hair- covered leaves come into touch with the skin, they produce histamine, which causes itching and burning. It is also common in Turkey and is used in both traditional medicine and the cooking. *Urtica dioica* includes several bioactive chemicals (Riehemann et al., 1999).

- ✓ Vitamins include C, A, K, and B group vitamins.
- ✓ Minerals include iron, magnesium, calcium, potassium, zinc, and phosphorus.
- ✓ Protein: The dried leaves have a significant protein content (25-30%).
- ✓ Antioxidants include flavonoids, carotenoids, and phenolic substances. Bioactive components include histamine, acetylcholine, serotonin, and chlorophyll.

Herbal medications made from crushed nettle stems, leaves, and seeds have been used orally and topically to treat eczema and psoriasis. People also cure eczema by boiling the entire plant and making infusions from the leafy branches, seeds, and shoots (Said et al., 2015).

2. CONCLUSION

Thousands of medicinal aromatic plant species are utilized for therapeutic purposes all over the world. There are many plants used to cure eczema, but this section focuses on the 10 most regularly used and well-known ones. There is no cure for eczema, and plant-based treatments are mostly intended to alleviate symptoms. These herbs are chosen for their ability to relieve irritation, reduce dryness, and create a calming sensation.

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CHAPTER XII

PHYTOTHERAPEUTIC STRATEGIES FOR RETINAL DISEASES

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INTRODUCTION

The eye is one of the organs with the highest metabolic rate. Inflammation can be observed in ocular tissues due to the accumulation of reactive oxygen species caused by photo-oxidation. In addition, the eye has been associated with many diseases, including cancer formation, depending on the presence of mutations. In addition, when looking at the pathophysiology of many ocular diseases, it is known that diseases caused by hypoxia, ischemia and diabetes can also develop (Xu et al., 2018). The aim is to prevent the formation of ocular diseases, reduce the development of the disease, apply highly effective treatment options and improve vision by minimizing vision-related defects. However, in some eye-related diseases, the damage in the eye may not be curable. In cases of retinal damage such as diabetic retinopathy (DR) and age-related macular degeneration (AMD), laser treatment, cryopexy and intravitreal application of drugs can be among the basic treatments (Piccardi et al., 2019). In addition to known medical applications for many eye-related defects from the past to the present, it is included in the literature that herbal treatments are also used. These herbal applications are especially striking in the Chinese pharmacopoeia. Although most plants are used by the public, the clinical efficacy of a large majority of such herbal drugs is still not fully known. The biological activity of therapeutic plants has been associated with the different sources of the plant, preparation methods, qualities and combinations. The value of such herbal medicinal plants is indispensable (Xu et al., 2018). The use of herbal medicines that can help with treatment is an effective strategy in protecting retinal damage, affecting apoptosis, improving retinal endothelial cells and preventing the formation of new blood vessels (Lian et al., 2015). It has been reported that many plants and their active ingredients may be effective in protecting against retinal-related diseases such as DR, AMD and retinal vasculature disorder (NVD) and play a role in alleviating retinal damage (Ansari-Mohseni et al., 2023).

1. RETINAL DISORDERS

The most risky ones within the scope of ocular diseases are considered to be retinal diseases. Because of the heterogeneous nature of these diseases, their complex pathogenesis and variety of etiology, it is known that they are associated with many different mechanisms including inflammation and cell dysfunction along with vascular abnormalities. Increased retinal damage can cause weakness in vision or blindness. As a result, among the categories of ocular disorders, retinal diseases have been highly concerning. The retina, where neuronal activity is intense, is highly sensitive to changes in its microenvironment. For this reason, irreversible damage can be observed in the retina. In addition, increased metabolic activities in the macula and increased oxygen demand are associated with oxidative stress (Country, 2017).

The maintenance of the retinal microenvironment is essential for the maintenance of retinal cell health. The blood retinal barrier (BRB) acts as an insulator to maintain this microenvironment. The inner and outer layers of the retina have inner BRB and outer BRB to provide permeability. These structures contribute to the efficient control of the retina through tight junctions. Many molecules are controlled by this transcellular traffic to cross the retina (Cunha-Vaz et al., 2011).

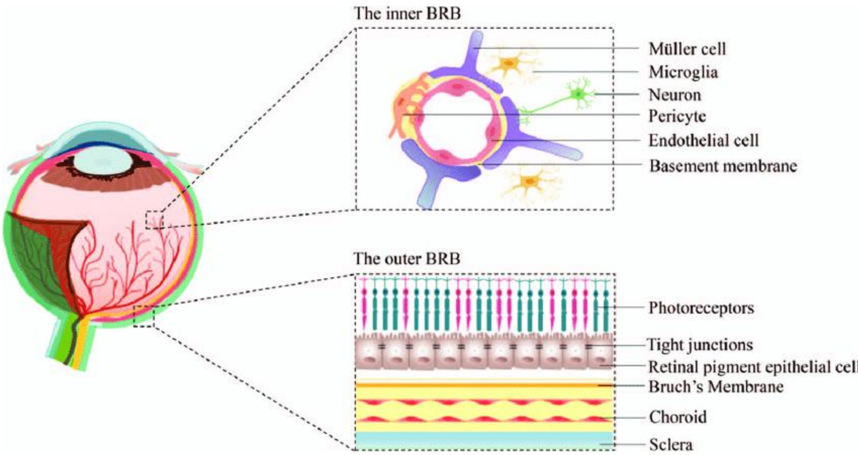

Figure 1. Demonstration of the inner and outer blood-retinal barrier (Yang et al., 2020)

BRB separates the retina from the systemic circulation. Thanks to the tight control of the transport of substances, retinal substance exchange is selectively maintained. At the same time, the passage of substances to the retina is facilitated. BRB facilitates the intake of necessary nutrients for the retina and meets metabolic needs. It also prevents the passage of harmful substances. In addition, any damage to BRB can lead to retinal diseases. As a result of damage to BRB, capillary leakage can be observed. Many complications such as retinal abnormalities and neurodegeneration can develop following this (Tisi et al., 2021). It may also result in edema and bleeding (Joussen et al., 2002). In the process where an ocular disease already begins to develop, the disease can rapidly progress from an early stage to an advanced stage with the increase in BRB damage. Understanding the molecular mechanisms of BRB damage is important for preventing and modifying the course of the disease (Bhutto and Lutty, 2012) (Luna et al., 1997; Zhang et al., 2014).

Herbal medicines and natural components are generally considered to be effective in many diseases, especially ocular, due to their positive aspects such as low toxicity and fewer side effects. In order to support drug development studies, it is necessary to know the mechanisms of action and biological activities of drugs. Studies have been conducted on many plants that may be therapeutic for retinal diseases, and many compounds have been obtained from natural herbal medicines. Puerarin, curcumin and *Lycium barbarum* polysaccharides (LBP) can be given as examples. In addition, many studies have focused on herbal medicines with high potential for BRB damage (Ansari-Mohseni et al., 2023).

2. THERAPEUTIC POTENTIAL OF MEDICINAL PLANTS IN VARIOUS RETINAL DISEASES

2.1. Age-related Macular Degeneration (AMD)

It has been reported that the tablet called Zhixue Quyu Mingmu Tablet (ZQMT), which contains many herbal ingredients, reduces bleeding caused by AMD and prevents lesion formation. It has also been found that ZQMT helps reduce the cost of Ranibizumab, which helps shorten the injection time. However, it has been proven that ZQMT is not effective in vision compared to ranibizumab (Jin et al., 2018). Huangban Bianxing One decoction (HBOD), which consists of eight herbal compositions, has been recorded to reduce lesions in AMD and also improve vision (Dan et al., 2019). A randomized double-blind study found that the herbal capsule containing *Radix scrophularia*, *Panax notoginseng*, *Astragali radix* and *Salvia miltiorrhiza* (Danshen) showed improvement in neovascularization-pigment epithelial detachment complex (CNV-PED) compared to the ranibizumab group (Pan et al., 2020). Focal electroretinogram (fERG) data were found to be significant in AMD patients given saffron, known as *Crocus sativus*. Accordingly, it was recorded that 20 mg of *Crocus sativus* increased visual acuity (Piccardi et al., 2012). In a clinical study in AMD where *Lycium barbarum L.* was applied at a dose of 13.7 g, it was determined that zeaxanthin levels were correlated with antioxidant capacity (Bucheli et al., 2011). According to a single-blind study, 15 g of Lycium barbarum L. was given to AMD patients. This amount was adjusted to be equivalent to 3 grams of zeaxanthin and lutein. Accordingly, it was reported that plasma zeaxanthin levels increased in individuals who received *Lycium barbarum L.* orally compared to those in the placebo group (Cheng et al., 2005).

2.2. Diabetic Retinopathy (DR)

Many plants and their components with potential effects have been investigated within the scope of DR. According to a study, the effects of crocin found in saffron on inflammation were investigated in 60 individuals with refractory diabetic maculopathy. The three groups included in the study were divided into patients who were given 5 mg crocin tablets, patients who received 15 mg and placebo. According to the results of the study, it was proven that crocin application helped to significantly reduce HbA1c and central macular thickness and increase visual acuity. It was determined that crocin had a neuroprotective role in patients with diabetic maculopathy and that it had antioxidant activity (Sepahi et al., 2018). In the study conducted by Forte et al., desmin, troxerutin, *Centella asiatica* and Melilotus were given to patients with macular cystoid edema. At the end of the study, it was noted that edema decreased compared to the control group (Forte et al., 2011). In a study involving 11 patients with diabetic macular edema (DME), 100 mg of curcumin supplement (Meriva®) was given twice daily for three months and the patients' OCT findings were evaluated. At the end of the study, it was determined that this supplement had no effect on visual acuity but reduced macular edema (Mazzolani et al., 2018). In a randomized controlled clinical trial, individuals with mild to moderate non-proliferative DR, and those without DR were given *DiVFuSS* supplements containing multiple herbal ingredients twice daily. They were also given a placebo. At the end of the six-month study, vision was reported to improve in those taking the supplements compared to the placebo group (Chous et al., 2016). In a study conducted by Zhao et al., the therapeutic efficacy of the herbal supplements Liuwei Dihuang and Ginkgo was evaluated in the context of diabetic complications. Both supplements were associated with a reduced prevalence of DR in patients with type 2 diabetes (Zhao, Yu, Liu, An, & Medicine, 2016). Steigerwalt et al. investigated the effect of a supplement called Pycnogenol® containing Pinus pinaster extract on DR. Accordingly, it was noted that DME decreased and vision improved in patients given Pycnogenol® three times a day. It was also reported that endothelial permeability and vascularity changed in a positive way. It was determined that this supplement was effective on retinal hemorrhage and hard exudates due to DR (Steigerwalt et al., 2009). According to another study conducted on DR, placebo and Qiming granules were applied to patients. Qiming granules are supplements containing *Radix Puerariae*, *Fructus Lyci*, *Radix Astragali* and *Radix Rehmanniae* extracts. According to the clinical data of the study, it was reported that there was a decrease in retinal arteriovenous circulation time in DR patients in the treatment group compared to the placebo group. Accordingly, it was predicted that hypoxia in the retina could be improved thanks to Qiming granules (Luo et al., 2009). The therapeutic efficacy of Danshen (*Salvia miltiorrhiza*) plant on DR has been tested. According to the study, Danshen supplement was given to DR patients three times a day for 24 weeks, and a placebo group was formed in which the supplement was not applied. According to the results, it was determined that Danshen improved the visual field and acuity (Dan et al., 2019; Lian et al., 2015). Zhao et al. reported that the plant Abelmoschus manihot has positive effects on vision in patients with NPDR. It is assumed that this effect is achieved by maintaining the functions of retinal cells, suppressing apoptosis and inhibiting blood vessel formation (Zhao et al., 2020).

2.3. Retinitis Pigmentosa

Studies on herbal therapies for retinitis pigmentosa are limited. In a study involving 42 patients, the *Lycium barbarum L.* plant supplement was administered orally for 12 months. It was determined that visual acuity increased in patients who were administered the *Lycium barbarum L* plant compared to the placebo group. It was also noted that the macula thinned in the placebo group. In addition, no side effects were observed due to the supplement (Chan et al., 2019).

2.4. Stargardt Disease

According to a clinical study, 20 mg of saffron was given to patients with Stargardt disease for 20 weeks. This double-blind, randomized, and placebo study suggested that saffron did not improve focal fERG but could slow the progression of the disease. (Piccardi et al., 2019).

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CHAPTER XIII

ROLE OF PHYTOCHEMICALS IN THE JAK-STAT SIGNAL TRANSDUCTION PATHWAY

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INTRODUCTION

A key intracellular network of communication, the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway controls cellular reactions to growth hormones, cytokines, and other stimulants from the environment. Numerous physiological functions, including the control of immunological responses, cell proliferation, differentiation, and death, depend on this system. However, autoimmune, inflammatory, and other types of cancer are linked to abnormalities in this pathway. Natural substances called phytochemicals are obtained from plants and are well-known for their anti-cancer, anti-inflammatory, and antioxidant qualities (Hu et al., 2022).

The JAK/STAT pathway's molecular targets, mechanisms of action, and possible applications in disease treatment are all covered in this chapter. The lack of findings in this field have been highlighted as is the potential for phytochemicals to be developed as next-generation therapeutic drugs that target the JAK/STAT the network. This chapter emphasizes the value of phytochemicals in JAK/STAT pathway and their contribution to the development of novel disease treatment strategies (Xue et al. 2023).

1. JAK/STAT PATHWAY

Cytokines activate the evolutionarily conserved JAK/STAT pathway, which carries external signals from the cell membrane to the nuclei and subsequently alters DNA transcription (O'Shea et al., 2015). By allowing cells to react to external stimuli, this mechanism controls a number of fundamental cellular functions, including differentiation, migration, apoptosis, and proliferation. Furthermore, JAK/STAT signaling is essential for regulating immune system activity (Banerjee et al., 2017; Villarino et al., 2017).

1.1. JAK Family

JAK1-JAK3 and non-receptor tyrosine-protein kinase (TYK2) are the four members of the JAK family. In cytokine communication, these kinases function as intracellular adaptor proteins (Roskoski Jr, 2016). Hematopoietic cells have a notably high amount of JAK3, whereas other JAK proteins are extensively expressed in a variety of tissue types (Barcia Durán et al., 2021). JAK proteins contain the FERM complex (four dot one, ezrin, radixin, and moesin), Src homology (SH2), kinase, and pseudokinase domains (Goult et al., 2010). When combined with the SH2 domain, the FERM domain—which includes substructures F1, F2, and F3—allows JAK to attach to receptors. By encouraging the kinase domain's phosphorylation and controlling its activity, the pseudokinase domain subsequently phosphorylates other downstream molecules (Lupardus et al., 2014). The seven different domains that make up JAK proteins are JH1-JH7 (Ferrao & Lupardus, 2017). The main cytokines that activate JAK proteins include growth factors, interferons and interleukins (Dodington, Desai, Woo, & Metabolism, 2018). The phosphorylation of the four JAK family proteins is catalyzed by the receptor tyrosine after the receptor-ligand complex activates the JAK proteins attached to the receptors. It controls several biological functions and interacts with cytokine receptors to activate specific STAT proteins (Rusiñol & Puig, 2023).

1.2. STAT Family

A crucial component of cellular signaling, STATs are found downstream of JAK kinases (Verhoeven et al., 2020). STAT1-STAT4, STAT5A-5B, and STAT6 are the seven members of the STAT family. These proteins include the helical and N-terminal domains, the linker domain, the DNA-binding domain, and the Src. It contains SH2 domain and the transcription activation domain and (Furqan et al., 2013). Nuclear transport and non-transport functions are regulated by the helical domain, whereas the N-terminal domain helps STAT proteins dimerize. As transcription factors, STAT proteins can attach to specific DNA sequences thanks to the DNA-binding domain (Chen et al., 2011). Through its recognition of phosphorylated tyrosine, the SH2 domain connects with specific cytokine receptors (Hong et al., 2022).

Following phosphorylation, cytosolic STAT proteins target the stimulated cytokine receptors. Dimers are created as a result of the phosphorylation of the tyrosine residues of STAT proteins. After reaching the nucleus, STAT dimers participate in transcription factor complexes to start target gene transcription (Baldini, Moriconi, Galimberti, Libby, & De Caterina, 2021). After being dephosphorylated in the nucleus, these proteins are released back into the cytoplasm (Li et al., 2023; Shih, 2022).

1.3. Negative Regulation of JAK-STAT Signaling

JAK/STAT signaling inhibited by many regulators (Yoshimura and Yasukawa, 2012). These regulators are divided into three primary categories: cytokine suppressors of signaling (SOCSs), protein tyrosine phosphatases and protein inhibitors of activated STATs (PIASs). The structural components of SOCSs include an SH2 domain and a SOCS cassette, and cytokines like interleukin 2 (IL-2), interleukin 3 (IL-3), and interferon-gamma (IFN-γ) can break them down (Liang et al., 2014; Yoshimura et al., 2007).

SOCSs may inhibit the entry of activated STATs into the nucleus, block STAT receptor binding, or inhibit JAKs (Kishimoto and Kikutani, 2001). By binding and ubiquitinating JAKs or STATs for destruction, proteasomal inhibits JAK-STAT signaling. A negative feedback loop that is fueled by the beneficial impact of active STATs on these molecules increases the transcription of SOCSs (Rytinki et al., 2009).

The proteins PIASx, PIASy, PIAS1 and PIAS3, which are members of the PIAS family, have the ability to either stop STAT dimers from forming or stop the dimers from attaching to DNA. Tyrosine can be dephosphorylated by protein tyrosine phosphatases, such as JAK, interacting with receptors. Furthermore, STAT dimers are directly cleaved by phosphatases. By dephosphorylating JAK/STAT, it can prevent its signaling (Pike and Tremblay, 2018; Wu and Zou, 2016).

2. BIOLOGICALLY ACTIVE PHYTOCHEMICALS

Phytochemicals are naturally found substances obtained from plants. A variety of these substances have demonstrated encouraging outcomes in treating human illnesses without causing any negative side effects. Biologically active substances with anticancer qualities are phytochemicals and their derivatives (Ding et al., 2023; Mandal et al., 2023). Different chemicals must be extracted, separated, and purified in order to develop anticancer drugs. Following isolation, these substances undergo additional testing in vivo and in vitro on a variety of cell lines. Plant selection, collection techniques, and drug formulation and application are all covered by traditional knowledge that has been passed down through the years. Since the 18th century, these medications have been utilized in a variety of formulations, decoctions, teas, and powders. Many other drugs have been obtained from plants, these plants have many pharmacological activities (Ciulla et al., 2003; Fridlender et al., 2015).

Chemical substances and phytochemicals with a wide range of medicinal uses (Shamsi et al., 2022). Despite being effective primary therapies, modern chemotherapy medications have a number of disadvantages. Researchers are therefore concentrating on therapies that have few adverse effects. By reducing a number of symptoms, phytochemicals can successfully target different forms of cancer and lessen their severity. They exert their chemoprotective function by controlling cancer-related signaling pathways. According to studies, this involves suppressing the epithelial-mesenchymal transition (EMT) and inducing apoptosis, which prevents cancer cells from spreading (Panda et al., 2017). Numerous signaling pathways, including the PI3K-mTOR pathway, nuclear factor kappa B (NF-κB) signaling, and the MAPK pathway, are disrupted by phytochemicals (Choy et al., 2019; Tewari et al., 2022). Additionally, phytochemicals impact the sensitivity of cancer stem cells to chemotherapy medicines. Additionally, by controlling different stages of cancer signaling mechanisms, phytochemicals demonstrate regulatory metabolic qualities in cancer cells (Selvaraji et al., 2019). These substances have the ability to influence mitochondrial pathways and membrane potential. Antioxidant, anti-diabetic, anti-inflammatory, analgesic, anticancer, neuroprotective, and antibacterial properties are only a few of the many therapeutic functions that phytochemicals demonstrate. They are a valuable resource for the creation and discovery of potent novel medications (Mihaylova and Popova, 2023).

3. PLANTS AND THEIR COMPOUNDS EFFECTIVE ON JAK/STAT PATHWAY

There are many herbal products and their derivatives that play a role in the JAK-STAT pathway. Many of these natural products have been shown to have inhibitory effects on the JAK/STAT pathway and to have therapeutic properties by affecting JAK/STAT related proteins. It is known that plants and their derivatives that are effective in this pathway are generally indirect. Examples of herbal components that are effective in the JAK/STAT pathway are capsaicin, emodin, withaferin A, aloin, thymoquinone, avicin D, paclitaxel, caffeic acid, cryptotanshinone, berbamine, evodiamine, cinnamon bark, honokiol and indirubin. The effectiveness of many plants and their components in various diseases is still in the research phase (Bose et al., 2020; Garg et al., 2021; Miklossy et al., 2013; Mohan et al., 2022).

3.1. Curcumin

Curcumin is a herbal compound found in Curcuma longa. Curcumin is known to have many therapeutic effects. Curcumin has been shown to affect molecules in the JAK/STAT pathway by causing changes in this pathway. In vitro evidence on glioblastoma and squamous carcinoma has been reported to inhibit STAT3 and induce apoptosis (Wu et al., 2013; Wu et al., 2015). In addition, according to other evidence, when STAT3 was inhibited by curcumin, an increase in the expression of PIAS3, SOCS1 and SOCS3, and a decrease in STAT3 and STAT6 was observed (Porro et al., 2019; Zhao et al., 2016). Curcumin analogues

FLLL11, FLLL12, FLLL32 and FLLL62 have many biological activities. It has been reported that STAT3 phosphorylation in melanoma cells is inhibited by these curcumin derivatives, and apoptosis is induced when STAT1 phosphorylation is induced by IFNγ (Bill et al., 2010).

3.2. Resveratrol

Resveratrol is a polyphenolic stilbenoid found in many fruits. Many biological activities of resveratrol have been investigated so far. Resveratrol shows its activity by targeting molecules in many ways. Resveratrol has been proven to have many therapeutic roles, including antioxidant, anti-inflammatory and anticancer (Malaguarnera, 2019). Resveratrol plays a role in the JAK/STAT pathway. For example, it has been reported that STAT1 and STAT3 phosphorylation is suppressed by resveratrol and immune system responses are modulated (Ma et al., 2015). According to a study conducted on SUP-B15, Jurkat and Kasumi-1 cell lines, it was reported that STAT3 was inhibited via IL-6 in leukemia cells treated with resveratrol, and in addition, cell cycle suppression and apoptosis were induced. It was also found that resveratrol increased survival in mice with leukemia (Li et al., 2010). When the disadvantage of resveratrol is evaluated, it is found that its bioavailability is low. 6-methyl-2-propylimino-6, 7-dihydro-5H-benzo[1,3]-oxathiol-4-one (LTR71) is a derivative of resveratrol. This derivative was applied to breast cancer cells and it was determined that STAT3 was suppressed. It has been reported that LTR71 increases the survival rate in mice with breast cancer (Kim et al., 2008).

3.3. Catechins

Flavans, another name for catechins, are members of the flavonoid group. Catechin is found especially in green tea. It is known that catechins have many biological activities, unique biochemical properties and high therapeutic potential. It has been proven that catechins can modulate many signaling pathways, including JAK/STAT (Singh et al., 2011). It has been reported that catechins suppress STAT1 and STAT3. It has also been proven that intercellular adhesion molecule 1 (ICAM-1) and inducible nitric oxide synthase (iNOS) are downregulated by catechins, thus demonstrating their anticancer effect (Senggunprai et al., 2014).

3.4. Oleanolic Acid

Oleanolic acid, found in many plants belonging to the Oleaceae family, is a triterpenoid compound with a pentacyclic structure. Oleanolic acid has shown its effect on the JAK/STAT pathway by modulating TYK2-STAT1/3 and reducing the dimerization of STAT3. It has been reported that the biological effects of many derivatives of oleanolic acid need to be evaluated on this pathway (Feng et al., 2020; Kim et al., 2013; Zhang et al., 2016).

3.5. Artemisinins

Artemisinins, a component of the Artemisia annua plant, are known to be therapeutically effective in reducing fever and malaria in Chinese traditional medicine. Artemisinins have been reported to have anti-cancer, anti-inflammatory properties and are effective in ocular diseases (Ho et al., 2014; Lu and Xie, 2019; Shi et al., 2015; Wong et al., 2017). In studies, STAT3 expression was suppressed by preventing dimer formation in cancer cells and pre-adipocytes (Ilamathi et al., 2016; Jang, 2016).

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