MEDICINAL AND ECONOMIC IMPORTANCE OF PLANTS

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PREFACE

Dear readers,

From the past to the present, people have used plants for nutrition, shelter, warmth, healing their wounds, and treating their diseases. Plants provide the oxygen and nutrients necessary to sustain human life and protect health. The use of plants in treatment began in the history of humanity. Thousands of years ago, humans discovered the therapeutic potential of plants and used them to maintain a healthy life. Many types of medicines used in modern medical science are also obtained from plants as well. Substances obtained from various parts of plants are used outside and within in the treatment of diseases, these plants are called medicinal plants. Today, these plants are used in areas such as phytotherapy, pharmacy, food, spices, cosmetics, dyes and also used as food and spices due to their aromatic properties. As technology progresses, the usage areas of these plants have increased, and they have been used in various industrial areas. Herbal treatment methods are today called 'alternative medicine or phytotherapy'. Phytotherapy; It is a systematic evaluation of medicinal plants, their traditional use, experimental observations, in vitro, in vivo, and clinical examination of therapeutic effects. Among all complementary therapies, phytotherapy is the one that receives the most scientific support. Herbal medicines include active ingredient parts of plants, herbal materials, herbal preparations, and herbal products. Phytotherapy is preferred by many societies around the world for the purpose of preventing and treating diseases. According to the investigations of WHO, there are approximately 20.000 plants used for medical purposes. Today, there has been an increase in the use of medicinal plants as humans move away from synthetic products containing chemical matter and turn to natural products. Many studies have shown that these plants have been used in every aspect of our lives from past to present. Due to increasing needs, the collection, drying, storage, and use of these plants from nature should be done in a controlled manner. Especially plant species with high economic value should be cultivated and natural farming of these plants should be started. These plants' diversity must be increased and chances of getting a share in foreign trade. All requirements to produce quality products by the standards required in the world must be fulfilled.

This book could be a helpful tool to understand where we are in the economic importance of plants in agriculture and medicine. We would like to thank all researchers and the İKSAD publishing house who contributed to the preparation of this book.

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CHAPTER 1

AN IMPORTANT MEDICINAL PLANT:

Helichrysum plicatum DC.

Prof. Dr. | Halil Erhan EROĞLU[1]

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INTRODUCTION

In Anatolia, people have been using plants for many years. Although plants have been used for a long time, the information about wild plants used in Anatolia is very limited. People often do not know the scientific plant names written in botanical books. On the other hand, most of the local plant names used by the people are not found in botanical books and dictionaries. The fact that different names can be given to the same plant in different regions of Anatolia causes a complexity in the recognition and use of plants (Eroğlu, 2008).

The scientific name of the genus *Helichrysum* Mill. is derived from the Greek words “helios” (sun) and “krysos” (gold). *Helichrysum* species have been used as tea in traditional folk medicine for a long time, especially due to their bile regulating properties and diuretic effects (Sezik et al., 2001). It is also used in kidney diseases and reduction of kidney stones, stomach and kidney pains, liver disorders, regulation of heartbeat, healing of burns and wounds, cracked hands and feet, jaundice, asthma diarrhea, and ear disorders (Tuzlacı, 1989; Eroğlu, 2008; Baytop, 2015). Due to this widespread use, it is known by different names in different regions of Anatolia. In genus *Helichrysum*, the most common local names are "ölmez çiçek", "sarı çiçek", "alay çiçeği", “yayla çiçeği”, “altın otu”, "herdemtaze", and "arı çiçeği". There are also local names specific to a single species, which are “beyaz kurna” (*Helichrysum pamphylicum* P.H.Davis & Kupicha), “püren” (*Helichrysum arenarium* (L.) Moench), “yoğurt çiçeği” (*Helichrysum orientale* (L.) DC., and “kırmızı guddeme” (*Helichrysum sanguineum* (L.) Kostel. (Eroğlu, 2018). In Europe, it is called "sun gold", "everlasting" (England), “fignamica”, “solfini”, and “elicriso” (Italy), “immortelle”, “strumblume”, and “strombloem” (Netherlads), “evöighedablomst” (Denmark), “immortelle”, “eternelle” (France), “koçanki” (Poland), “cmin” (Russia), and “molec”, “smill”, and “neven” (Czech Republic) (Aslan, 1994; Eroğlu, 2018).

The taxonomic features of the genus *Helichrysum* are as follows. Lanate, tomentose or glandular, perennial, suffruticose or herbaceous. Leaves simple, entire, linear to oblanceolate or alternate. Capitula corimbus at the tip, discoid or disciform, from the globose to obpramidala or cylindrical, 3-12 mm long, pluricerate, almost irregular to very regular imbricate, white-straw coloured, yellow, orange, or red, scarious. Receptaculum (flower tray) flat, bare. Flowers yellow, completely hermaphrodite or marginal flowers female; corollas tubular (tubular), 5-fid (piece), overly glandular. Achenes cylindrical, ± glandular. Pappus feathers yellowish, large-celled, from scabrose to barbellata (Davis and Kupicha, 1975).

The taxonomic status of the genus *Helichrysum* is as follows.

Division:	Spermatophyta
Subdivisio:	Angiospermae
Classis:	Dicotyledoneae (Magnoliopsida)
Subclass:	Asteridae
Ordo:	Asterales
Family:	Asteraceae
Genus:	*Helichrysum*

1. *Helichrysum plicatum* DC.

The plant is glandular, subglabrous to lanate-tomentose. Flowering stems rise from erect or (rarely) oblique, 4-42 cm, woody branched horizontal stems. Sleeping buds are usually absent. Basal leaves linear-oblanseolate, 10-100 × 2-10 mm; stem leaves subampleksicaul, linear-oblanceolate to linear, 15-70 × 2-20 mm. Capitula from subglobose to hemispherical, 4-9 mm. Fillari obtus to acute, ± irregular and rarely imbricate, often longitudinally coiled, yellow, or cream. All flowers hermaphrodite or marginal female. Flowering; 6-8 (Davis and Kupicha, 1975).

1. Plants subglabrose; stem leaves 40-70 × 2-20 mm, yellowish green………………………………………………………... subsp. *polyphyllum*

1. Plants lanate-tomentose from sparse to dense; stem leaves 15-40 × 2-5 mm, whitish or greyish green

2. Involucrum cream-colored………………. **subsp. *pseudoplicatum***

2. Involucrum yellow……………………………… **subsp. *plicatum***

Helichrysum plicatum* subsp. *plicatum is found in *Pinus nigra* J.F. Arnold and *Abies cilicica* (Antoine & Kotschy) Carrière forests, bushes, rocky slopes, 1400-2850 m (Figure 1).

Helichrysum plicatum* subsp. *polyphyllum (Ledeb.) P.H.Davis & Kupicha is found in *Abies cilicica* forest, rocky slopes, steppe and flowing stony areas, 1500-2800(-3500) m (Figure 2).

Figure 1: The general view of *Helichrysum plicatum* subsp. *plicatum* (Hamzaoğlu 4217, Yozgat) (Eroğlu, 2008).

Figure 2: The general view of *Helichrysum plicatum* subsp. *polyphyllum* (Hamzaoğlu 4769, Adana) (Eroğlu, 2008).

Helichrysum plicatum* subsp. *pseudoplicatum (Náb.) P.H.Davis & Kupicha is found on rocky slopes, 1800-2500 m (Figure 3).

Figure 3: The general view of *Helichrysum plicatum* subsp. *pseudoplicatum* (Budak 2223, Bitlis) (Eroğlu, 2008).

Helichrysum plicatum is one of the most widely used species of the genus *Helichrysum* for medicinal purposes in Anatolia. As in the general genus, *Helichrysum plicatum* is also named with different local names in different regions and differs in medical use (Table 1).

The diploid chromosome number of the species is 2*n* = 32, and the karyotype formula is 16m, consisting entirely of metacentric chromosomes (Figure 4). It has a symmetrical karyotype in terms of karyotype asymmetry (Azizi et al., 2014).

Due to its widespread use, there are many studies on the chemical composition and bioactive properties of the species. With these studies, attention was drawn to the important benefits of the plant as well as the situations that require careful use.

Table 1: The local names given to *Helichrysum plicatum* in Anatolia and its medicinal use.

Local name	Province	Medical use	References
Arı çiçeği Bozoğlan Yayla çiçeği	Kütahya Mersin Erzurum	Urine and bile enhancer and stone reducer	Baytop, 2015
Altın otu Herdemtaze	Isparta	Medical	Özçelik et al., 2006
Ölmez çiçek	Bingöl		Malak, 2007
Ölmez çiçek	Hatay	Medical tea	Ayanoğlu et al., 2002
Sarılık çiçeği	Bolu, Bilecik	Jaundice and stomach ailments Wound healer	Çubukçu, 2002 Sezik et al., 2000
	Gümüşhane	Wounds and burns	Tabata et al., 1998
	Tokat	Treatment of hand and foot cracks	Tabata et al., 1998
	Amasya Osmaniye Mersin Isparta Karaman Kütahya	Diuretic and kidney stone reducer	Tabata et al., 1998
	Antalya	Earache	Tabata et al., 1998
Ölmez çiçek Altın otu	Gaziantep		Özuslu, 2005
Altın çiçeği Arı çiçeği Bozoğlan Herdem güzeli Herdemtaze Kaymak çiçeği Koyungözü Sarı çiçek Sarılık çiçeği Savran Yayla çiçeği Çıngrak çiçeği			Tuzlacı, 2011

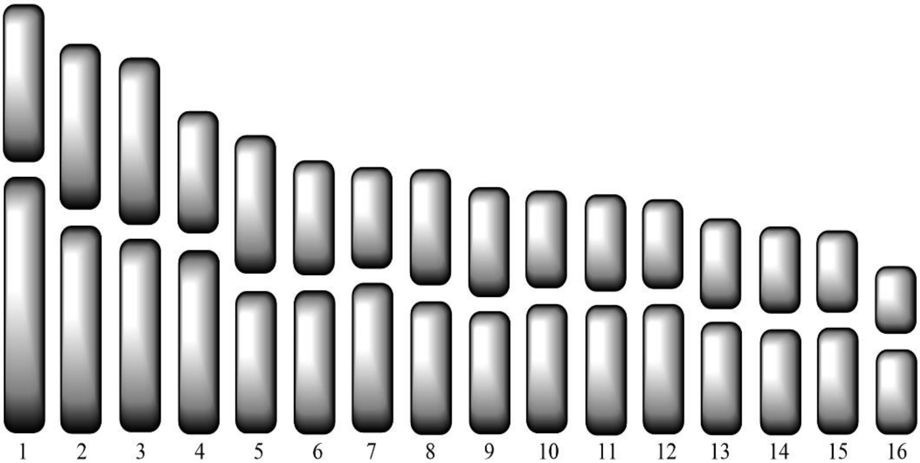

Figure 4: The monoploid ideogram of *Helichrysum plicatum*.

1.1. Chemical Composition

Albayrak et al. (2010) analyzed the methanol extracts of some *Helichrysum* species naturally grown in Anatolia by GC/MS. The main phenolic components of *Helichrysum plicatum* subsp. *pseudoplicatum* are chlorogenic acid, caffeic acid, ferulic acid, p-coumaric acid, p-hydroxybenzoic acid, syringic acid, apigenin, apigenin-7-glucoside, epicatechin, hesperidin, luteolin, and naringenin.

Bigović et al. (2011) analyzed the flower extracts of *Helichrysum plicatum*. The main phenolic components are free aglycones (apigenin, kaempferol, and naringenin) and glycosides (apigenin, kaempferol, and naringenin, and quercetin).

Bigović et al. (2017) analyzed the dry flower heads of *Helichrysum plicatum* by HPLC-DAD. The main phenolic components are free aglycones (apigenin, kaempferol, and naringenin), glycosides (apigenin, kaempferol, and naringenin, and quercetin), chalcone derivates, and chlorogenic acid.

Vujić et al. (2020) identified 142 compounds from compound classes such as pyrones, flavonoids, terpenoids, phloroglucinols, phthalides, and acetophenones in the aerial parts of *Helichrysum plicatum*.

The phenolic compounds of isoquercitrin, luteolin, naringerin, dicaffeoylquinic acid, and chlorogenic acid in *Helichrysum plicatum* subsp. *plicatum* (Taşkın et al., 2020) and gallic acid in *Helichrysum plicatum* subsp. *pseudoplicatum* (Miloğlu et al., 2023).

1.2. Antibacterial Activity

Today, the effects of different components of traditional medicinal plants on microorganisms have been intensively investigated to identify natural substances as new antibacterial agents, and these studies are continuing. In this context, many studies have been conducted with extracts of *Helichrysum plicatum*.

Aslan et al. (2007) investigated the antibacterial activity of ethyl alcohol and petroleum ether extracts of some species of *Helichrysum* on gram-positive (*Bacillus cereus, Bacillus megaterium, Micrococcus luteus, Listeria monocytogenes, Staphylococcus aureus,* and *Streptococcus mutans*) and gram-negative (*Escherichia coli, Pseudomonas aeruginosa, Shigella sonnei,* and *Salmonella enteritis*) bacteria. The ethyl alcohol extract of *Helichrysum plicatum* subsp. *plicatum* together with *Helichrysum armenium* DC. subsp. *armenium*, *Helichrysum graveolens* (M.Bieb.) Sweet, and *Helichrysum pallasii* (Spreng.) Ledeb. showed strong antibacterial potential.

Demir et al. (2009) investigated the antibacterial activity of ethyl alcohol and water extracts of the leaves and flowers of *Helichrysum plicatum* subsp. *plicatum* on *Escherichia coli* O157:H7. The flower ethyl alcohol extract showed strong antibacterial potential.

Albayrak et al. (2010) investigated the antibacterial activity of methanol extracts of *Helichrysum plicatum* subsp. *pseudoplicatum*. The methanol extract showed antibacterial potential on *Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus, Bacillus cereus, Bacillus brevis,* and *Aeromonas hydrophila* and did not show on *Escherichia coli, Morganella morganii, Yersinia enterocolitica, Proteus mirabilis*, and *Mycobacterium smegmatis*.

Vujić et al. (2020) investigated the antibacterial activity of dichloromethane, ethyl alcohol, and sunflower oil extracts of *Helichrysum plicatum* on eight bacteria. The extracts showed notable antibacterial potential.

Taşkın et al. (2020) investigated the antibacterial activity of chloroform, methanol, and petroleum ether extracts of *Helichrysum plicatum* subsp. *plicatum* on *Klebsiella pneumoniae*, *Proteus mirabilis, Pseudomonas* *aeruginosa*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*. The methanol extract showed strong antibacterial potential than other extracts.

Duran et al. (2023) investigated the antibacterial activity of methanol extract of *Helichrysum plicatum* subsp. *polyphyllum* on gram-positive (*Bacillus subtilis, Bacillus cereus,* and *Staphylococcus aureus*) and gram-negative (*Salmonella enteritidis, Klebsiella pneumoniae*, and *Escherichia coli*) bacteria. The methanol extract of *Helichrysum pl*icatum subsp. *polyphyllum* showed strong antibacterial potential against *Bacillus cereus* (gram-positive) and *Salmonella enteritidis* (gram-negative).

1.3. Antimicrobial Activity

Albayrak et al. (2010) investigated the antimicrobial potential of methanol extracts of *Helichrysum plicatum* subsp. *pseudoplicatum* on yeast. The methanol extract showed antibacterial potential on *Saccharomyces cerevisiae*.

Bigović et al. (2017) investigated the antimicrobial activity of ethyl alcohol extract of *Helichrysum plicatum* on yeast. The ethyl alcohol extract of *Helichrysum plicatum* showed strong antimicrobial potential against *Candida albicans*.

Vujić et al. (2020) investigated the antimicrobial activity of dichloromethane, ethyl alcohol, and sunflower oil extracts of *Helichrysum plicatum* on one fungus and two yeast. The extracts showed strong antimicrobial potential.

Taşkın et al. (2020) investigated the antimicrobial activity of chloroform, methanol, and petroleum ether extracts of *Helichrysum plicatum* subsp. *plicatum* on *Candida albicans*. The methanol extract showed strong antimicrobial potential than other extracts.

Duran et al. (2023) investigated the antimicrobial activity of methanol extract of *Helichrysum plicatum* subsp. *polyphyllum* on yeast. The methanol extract of *Helichrysum plicatum* subsp. *polyphyllum* showed strong antimicrobial potential against *Candida albicans*.

1.4. Antioxidant Activity

Antioxidant is the general name of the group of compounds that stop or slow down the oxidation reactions caused by free radicals. These compounds neutralize free radicals, prevent the body from being affected by them and enable it to renew itself. Therefore, antioxidants, especially from medicinal plants, are widely used in the food industry as potential inhibitors of lipid peroxidation due to their many health benefits (Deng et al., 2011). Various *in vitro* test systems are used for the discovery of compounds of natural origin and synthetic origin with antioxidant effects.

Aslan et al. (2007) investigated the antioxidant activity of ethyl alcohol extract of *Helichrysum plicatum* subsp. *plicatum* in streptozotocin-induced rats. The ethyl alcohol extract showed strong antioxidant potential.

Albayrak et al. (2010) investigated the antioxidant activity of methanol extract of four *Helichrysum* taxa by phosphomolybdenum assay and 2,2-difenil-1-pikrilhidrazil (DPPH) radical scavenging. *Helichrysum plicatum* subsp. *pseudoplicatum* showed strong antioxidant potential than *Helichrysum arenarium* (L.) Moench subsp. *erzincanicum* Davis & Kupicha, *Helichrysum arenarium* subsp. *rubicundum* (C.Koch.) Davis & Kupicha, and *Helichrysum armenium* subsp. *araxinum* (Kirp.) Takht.

Bigović et al. (2011) investigated the antioxidant activity of ethyl alcohol extract of *Helichrysum plicatum* by DPPH radical scavenging. The extract of *Helichrysum plicatum* showed strong antiradical activity.

Vujić et al. (2020) investigated the antioxidant activity of dichloromethane, ethyl alcohol, and acetonitrile extracts of *Helichrysum plicatum* by DPPH radical scavenging. The extracts of dichloromethane and ethyl alcohol showed the most potent antioxidant activity.

Taşkın et al. (2020) investigated the antioxidant activity of chloroform, methanol, and petroleum ether extracts of *Helichrysum plicatum* subsp. *plicatum* by DPPH radical scavenging, trolox equivalent antioxidant activity, and ferric reducing antioxidant power assay. The methanol extract showed strong antioxidant potential than other extracts.

Kaya (2022) investigated the antioxidant activity of acetone, chloroform, ethyl alcohol, hexane, and water extracts of *Helichrysum plicatum* by DPPH radical scavenging, cupric reducing antioxidant capacity (CUPRAC), and 2,2′-Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) assay (ABTS). It was determined that the antioxidant activities of the extracts of *Helichrysum plicatum* obtained with different solvents were lower than the standard antioxidant substances. On the other hand, water extract in CUPRAC and DPPH methods and ethyl alcohol extract in ABTS method showed higher antioxidant activity than other extracts.

Miroğlu et al., (2023) investigated the antioxidant activity of methanol extract of *Helichrysum plicatum* subsp. *pseudoplicatum*. The methanol extract showed strong antioxidant potential.

1.5. Antidiabetic Activity

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia, micro and macrovascular diseases, caused by impaired insulin secretion or insulin activation, causing disturbances in carbohydrate, fat and protein metabolism in the body. After a long period of metabolic disorders, specific complications of diabetes can occur, and atherosclerosis accelerates. Depending on the severity of the metabolic abnormality, diabetes may be asymptomatic or symptomatic (thirst, polyurea, weight loss) or may progress to ketoacidosis and coma (Kuzuya et al., 2002).

Aslan et al. (2007) investigated the antidiabetic activity of ethyl alcohol extract of *Helichrysum plicatum* subsp. *plicatum* in streptozotocin-induced rats. The ethyl alcohol extract showed strong antidiabetic potential.

1.6. Wound Healer

The basic principle of wound healing is to minimize tissue damage, to ensure adequate tissue perfusion and oxygenation, as well as proper nutrition and moistening of the tissue. The wounds are classified as partial and full thickness wounds, as well as acute and chronic wounds, open and closed wounds (Özkorkmaz and Özay, 2009).

Sezik and Aslan (2000) reported the wound healer potential of *Helichrysum plicatum* subsp. *plicatum*.

Miroğlu et al., (2023) investigated the wound healer effect of the methanol extract of *Helichrysum plicatum* subsp. *pseudoplicatum*. The methanol extract showed strong wound healer potential by increasing cell migration at 12 hours and significantly closing the wound area at 24 hours.

1.7. Anti-urease Activity

Urease is a nickel-containing enzyme that catalyzes the hydrolysis of urea to ammonia and carbon dioxide. Urease is present in many plants, algae, fibrous fungi, and bacteria and plays an important role in the nitrogen cycle in nature (Lubbers et al., 1996). Urease is used in clinical studies such as removing urea from the blood in dialysis machines and determining the amount of urea in the blood, and cleaning urea in wastewater (Krajewska, 2001).

Taşkın et al. (2020) investigated the anti-urease activity of chloroform, methanol, and petroleum ether extracts of *Helichrysum plicatum* subsp. *plicatum*. The maceration methanol extract showed strong anti-urease potential than other extracts.

1.8. Anticholinesterase Activity

Substances that inhibit the acetylcholinesterase enzyme are called cholinesterase inhibitors or anticholinesterases. This mechanism is anticholinesterase activity.

Taşkın et al. (2020) investigated the anticholinesterase activity of chloroform, methanol, and petroleum ether extracts of *Helichrysum plicatum* subsp. *plicatum*. The Soxhlet methanol extract showed strong anticholinesterase potential than other extracts.

1.9. Anti-inflammatory Activity

Anti-inflammatory activity is the effects of reducing inflammation and edema with natural or synthetic substances. Anti-inflammatory agents aim to reduce pain by reducing inflammation.

Karaca et al. (2009) investigated the anti-inflammatory effect of the diethyl ether extract of *Helichrysum plicatum* in carrageenan-induced inflammation in rats. The diethyl ether extract showed strong anti-inflammatory potential.

Taşkın et al. (2020) investigated the anti-inflammatory effect of chloroform, methanol, and petroleum ether extracts of *Helichrysum plicatum* subsp. *plicatum*. All methanol extracts showed very close anti-inflammatory activity to each other.

1.10. Antimutagenic Activity

A mutagenic effect is a permanent base change in the genetic material that occurs spontaneously or by any chemical agent. The increase in mutation-induced diseases and cancer cases in recent years has made it necessary to investigate anticarcinogen and antimutagen substances. Although not every mutagenic agent causes cancer, mutation analyzes are among the pioneering studies in cancer research, which is the disease of our age, due to the possible parallel relationship between mutagenicity and carcinogenicity (Loh et al., 2009).

Özbek et al. (2009) investigated the antimutagenic activity of methanol extract of *Helichrysum plicatum* subsp. *plicatum* by AMES-*Salmonella*/microsome assay in TA1535 and TA1538 strains of *Salmonella typhimurium*. The methanol extract showed antimutagenic potential on TA1535 strain and did not show on TA1538 strain.

1.11. Cytotoxic and Genotoxic Effects

The cytotoxic effect is the toxic effect of natural or synthetic chemicals on the cell, killing the cell or disrupting its function. The genotoxic effect is defined as the chemicals that cause mutation by interacting with the enzymes that ensure the replication of DNA or the genome, causing damage to the DNA and causing mutation. In genetic toxicology studies, changes in DNA molecules are examined and genetic damage caused by various agents is evaluated. Genetic toxicity includes damage to the nucleus, chromosome, and DNA structure such as DNA insertions, DNA breaks, gene mutations, chromosomal abnormalities, clastogenicity and aneuploidy (Eroğlu, 2008).

It is investigated the genotoxic and antimitotic activities of methanol extract and herbal teas of *Helichrysum plicatum* subsp. *plicatum*, *Helichrysum plicatum* subsp. *polyphyllum*, and *Helichrysum plicatum* subsp. *pseudoplicatum* on human lymphocyte cultures. All extracts of all taxa showed antimitotic effect and genotoxic potential in high concentrations (Eroğlu, 2008; Eroğlu et al., 2009; Eroğlu et al., 2010a; Eroğlu et al., 2010b).

Bigović et al. (2011) investigated the cytotoxic activity of ethyl alcohol extract of *Helichrysum plicatum* in K562, HeLa, and PC3 human cancer cell lines. The ethyl alcohol extract showed cytotoxic potential against K562 and PC3 cells.

Duran et al. (2023) investigated the cytotoxic activity of methanol extract of *Helichrysum plicatum* subsp. *polyphyllum* on CCD-18Co and DLD-1 human cancer cell lines by MTT assay. The methanol extract of

Helichrysum plicatum subsp. *polyphyllum* showed cytotoxic potential against DLD-1 cell lines.

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CHAPTER 2

AMLA (*Phyllanthus emblica*) AND ITS MEDICINAL IMPORTANCE

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INTRODUCTION

Amla, a deciduous tree of the Euphorbiaceae family, bears edible fruits mainly found in India, Southeast Asia, China, Iran, and Pakistan. In traditional medicine, amla alleviates anxiety, skin and ocular discomfort, anemia, male reproductive health, digestion, liver health, and cardiovascular well-being (Ramakrishna et al., 2020). Its fruits, renowned in botanical circles, are extensively employed in medicinal, culinary, and cosmetic domains. Rich in phenolic compounds, amla is a valued natural source of antioxidants, nutraceuticals, and medicinals. With an appealing flavor and aroma, amla fruit is esteemed by consumers. Both animal and human studies corroborate amla's anti-hyperglycemic, hypoglycemic, anti-inflammatory, anti-hyperlipidemic, and antioxidant properties. Abundant antioxidants, including gallic acid, ascorbic acid, and phenolic compounds, endow amla with immune function and digestion benefits.

Amla, a native tree of Southeast Asia, yields fruits rich in bioactive compounds, attracting attention for their exploration of naturally occurring biologically active substances. Research has indicated that the fruits and various parts of the amla tree prominently contain polyphenols and vitamin C. These constituents, namely polyphenols and vitamin C, substantially contribute to crucial antioxidant activities, accompanied by significant in vivo effects such as augmented antioxidant status and reinforced endogenous antioxidant defense mechanisms. Moreover, amla demonstrates potential health advantages encompassing anti-hyperlipidemic and antidiabetic properties while exhibiting anticancer, anti-inflammatory effects, safeguarding the digestive tract, and conferring neuroprotective attributes. The encouraging outcomes from investigations into amla's bioactive compounds provide substantial backing for their potential capacity to foster health and avert ailments.

1. COMPOSITION

Amla fruits are a substantial source of carbohydrates, surpassing 70 g per 100 g of dry weight (D.W.). Fiber content ranges from 7.2-16.5 g per 100 g D.W. Beyond carbohydrates and fiber; amla fruits comprise protein, minerals, and fats. Mineral content, including iron, calcium, and phosphorus, varies from 2.0-4.5 g, 2.1-3.1 g, and 0.2-0.6 g per 100 g D.W., respectively. Variations stem from cultivar disparities, confirmed by extensive investigations. Notably, ascorbic acid, vitamin C, is pivotal in amla fruits. Research on various amla varieties reports values from 193-720 mg per 100 g of fruit. Though an optimal daily vitamin C intake remains undefined due to evolving societal factors, global health authorities have set Recommended Dietary Allowances (RDAs) between 40 and 110 mg/day. Australian and Chinese health authorities propose 190–220 mg/day. Meeting these recommendations, a serving of 100 g of fresh amla fruits (2–3 pieces) fulfills daily vitamin C requirements. Remarkably, amla juice exhibits higher vitamin C content than other fruits like apples, lime, pomegranate, and select grapes. Alongside vitamin C, amla fruits harbor significant nutritional compounds, including vitamins A, B1, and E, at 290 IU, 30 mg/100 g, and 0.17 mg/100 g. Amla fruits also offer valuable calcium and iron, providing 25 mg and 1 mg per 100 g of fruit, respectively.

2. PHYTOCHEMISTRY

Amla (*Phyllanthus emblica*) exhibits diverse phytochemical composition across its plant parts: fruits, leaves, and branches. Notably, polyphenols dominate, encompassing phenolic acids, flavonoids, tannins, and derivatives, driving amla's bioactivity. Phenolic acids like hydroxybenzoic acids (4-hydroxybenzoic acid, coumaric acid, etc.) prevail in fresh fruits and commercial products, while leaves and branches are abundant in gallic acid. Hydroxycinnamic acids, including caffeic and chlorogenic acids, are found in amla fruits. Flavonoids, notably flavonols (e.g., kaempferol, quercetin), flavones (e.g., apigenin, luteolin), flavanones, and flavan-3-ols, are prominent. Flavonols (e.g., kaempferol and its derivatives) are distributed in various plant sections. Quercetin derivatives are found in fruits, leaves, and branches. Flavones like apigenin, luteolin, and myricetin are in fruits and commercial products; myricetin 3-O-rhamnoside occurs in leaves and branches. Flavanones and flavan-3-ols (e.g., eriodictyol, naringenin, and their derivatives) are exclusive to leaves and branches, as are flavan-3-ols like epigallocatechin, epigallocatechin 3-O-gallate, and gallocatechin. Tannins, another substantial phenolic group, exist in amla's fruits, leaves, and branches. Ellagitannins encompass chebulinic acid, chebulagic acid, and emblicanin A and B, among others. Ellagic acid derivatives are also present. Hydrolyzable tannins and phlorotannins are prevalent in leaves and branches. Tannic acid appears in fruits. Additional phenolic compounds like 2,4-di-tert-butylphenol and Phenol, 3,5-bis (1,1-dimethyl ethyl), along with alkaloids (e.g., phyllantine, phyllantidine), contribute to amla's phytochemical profile (Ur-Rehman et al. 2007).

3. MEDICINAL SIGNIFICANCE

3.1. Antioxidant Activity

Numerous studies across in vitro, in vivo, and human contexts substantiate the potent antioxidant potential of *Phyllanthus emblica* fruit constituents. In vitro investigations emphasize the role of polyphenols in conferring high antioxidant activity, notably by scavenging radicals like 1,1-diphenyl and 2-picrylhydrazyl (DPPH). Other chemical assays, including ABTS, nitric oxide (NO) radical scavenging, Ferric Reducing Antioxidant Power (FRAP), and low-density lipoprotein (LDL) oxidation, further confirm amla's antioxidant capacity. Amla's polyphenols effectively neutralize superoxide anion and hydroxyl radicals and chelate iron (III), strengthening the body's antioxidant defense system. This system encompasses non-enzymatic compounds like glutathione (GSH) and enzymes such as catalase (CAT), GSH reductase, glutathione peroxidase (GPx), and superoxide dismutase (SOD). Together, these components synergistically counteract oxidative stress, preserving cellular redox equilibrium and thwarting potential damage in living organisms. Amla-derived bioactive compounds reinforce antioxidant defenses and curb oxidative harm in diverse cell lines, suggesting their therapeutic potential against oxidative stress-related conditions.

Various studies highlight amla's impact on oxidative damage in cellular, animal, and human models. Notably, extracts up to 100 μg/mL exhibit robust antioxidant activity and stimulate antioxidant defense mechanisms without notable cytotoxicity. Higher concentrations (200 μg/mL) are needed to effectively reduce reactive oxygen species (ROS) levels and enhance cell survival in myoblasts (Yamamoto et al. 2016).

In animals, amla's protective influence against oxidative damage is evident. Administration of amla fruit extract (500 mg/kg body weight) for 28 days increased vital antioxidant enzymes and decreased lipid peroxidation in mice's thymus (Singh et al. 2013). Similar effects were observed in mice exposed to arsenic toxicity and diabetic mice, where amla extract mitigated oxidative stress and bolstered antioxidant enzyme activities (Saha et al. 2015; Reddy et al. 2010).

Human trials reinforce amla's antioxidant potential. Smokers consuming amla fruit extract experienced reduced peroxidation and enhanced antioxidant status (Biswas et al. 2014). Clinical trials involving individuals with metabolic syndrome showed reduced lipid peroxidation and induced GSH levels with amla extract consumption (250–500 mg capsules) (Biswas et al. 2013). These findings collectively highlight amla's ability to limit oxidation, enhance antioxidant status, and stimulate the endogenous antioxidant defense system. Amla's potential in managing oxidative damage induced by lifestyle factors or diseases like metabolic syndrome is promising. Beyond antioxidant activity, amla's polyphenols exhibit diverse biological effects.

3.2. Cardio Protective Activity

Amla's bioactive compounds hold promise for managing hyperlipidemia and mitigating cardiovascular disorders. Studies demonstrate amla juice's capacity to inhibit oxidized low-density lipoprotein (LDL) uptake in macrophages, significantly reducing LDL cholesterol oxidation by 90%. Amla polyphenols, like emblicanin A and B, punigluconin, and pedunculagin, limit fibrosis formation in the cardiovascular tissues of mice subjected to ischemia and reperfusion. Amla supplementation in young goats reduces LDL, cholesterol, and blood glucose levels. Hydroalcoholic amla extract lowers arterial mean blood pressure and enhances the antioxidant system in hypertensive mice. Additionally, polyphenol-rich amla extracts mitigate metabolic changes from excessive fructose intake, reducing triglycerides, cholesterol, and related markers while modulating essential proteins in lipid metabolism and inflammation. These findings suggest amla's potential in managing hyperlipidemia and cardiovascular disorders through lipid regulation, antioxidant activity, and protein modulation. In humans, amla extract intake reduces high-sensitive C-reactive protein, total cholesterol, and LDL levels in obese subjects.

3.3. Antidiabetic Activity

Amla and its bioactive compounds exhibit antidiabetic potential. Ellagic acid and ascorbic acid in amla reduce key glucose digestion enzymes in vitro. Freeze-dried amla extract reduces serum glucose and triglyceride levels in diabetic mice, and amla juice improves serum glucose and insulin levels. A phytochemical extract from amla leaves increases serum insulin and reduces glucose in diabetic mice. Clinical trials demonstrate amla's ability to reduce blood glucose levels in diabetic patients. Amla extract also shows the potential to reduce the risk of neuropathy in diabetic patients. These findings highlight amla's role in diabetes management and restoration of glucose and insulin levels.

3.4. Anticancer Activity

Amla's polyphenols exhibit anticancer effects through nonclinical and clinical studies. Amla extracts induce apoptosis and inhibit proliferation in cancer cells. Pyrogallol, amla's polyphenol, induces cell cycle arrest and modulates apoptotic markers in lung cancer cell lines. In conclusion, amla and its bioactive compounds hold the potential to manage hyperlipidemia, diabetes, and cancer. These findings underscore the need for further research to elucidate mechanisms and extend our understanding of amla's therapeutic applications.

3.5. Anti-inflammatory Activity

Amla's phytochemistry demonstrates potential anti-inflammatory activity, though current evidence is limited. Li et al. (2020) studied amla extract (rich in gallic acid, corilagin, and ellagic acid) on RAW 264.7 cells. During lipopolysaccharide-induced inflammation, treatment reduced inflammatory markers (nitric oxide, TNF-α, IL-1β, IL-6). Similarly, a study on animals exposed to arsenic showed amla extract (500 mg/kg) lowered TNF-α, IL-1β, and IL-6 levels and reduced paw edema. P. emblica L. extract acted like a nonsteroidal anti-inflammatory drug (Dang et al. 2011). Human research explored amla's anti-inflammatory potential. Diabetic subjects consuming P. emblica L. fruit extract (500 mg/day) showed reduced platelet aggregation (Fatima et al. 2014). These findings suggest amla's anti-inflammatory effects in cells, animals, and humans, indicating therapeutic use. Further research is needed for a comprehensive understanding of mechanisms.

3.6. Digestive Tract Protection

Polyphenols from P. emblica L. show potential in safeguarding gastrointestinal organs. Notably, amla compounds may inhibit clarithromycin-resistant Helicobacter pylori strains, a cause of gastric ulcers (Mehrotra et al. 2011). Animal studies by Al-Rehaily et al. (2012) found that P. emblica L. extract (250 and 500 mg/kg) reduced gastric secretion, ulcer index, bleeding, and lesions in various ulcer-inducing methods. In mice with non-alcoholic fatty liver disease induced by high-fat diets, amla improved adiponectin activity and PPAR-α expression (Huang et al. 2017). Using P. emblica L. in L-arginine-induced pancreatitis reduced lipase and IL-10 levels and improved pancreatic health. Amla extract also lessened colon histological changes in acetic acid-induced colitis mice (Dang et al. 2011). Amla extract consumption (500 mg/tablet, twice daily) eased gastroesophageal reflux symptoms. These studies reinforce amla's organ-protective effects, supported by modern medicine, aligning with traditional practices.

3.7. Neurological Protection

Amla's bioactive compounds potentially shield against neurological changes, particularly in Alzheimer's disease. Administering amla extract (100 mg/kg; high in emblicanin A and B) for 60 days reduced neurotoxicity induced by aluminum chloride in mice (Bharathi et al. 2018). It improved apoptotic mechanisms, acetylcholinesterase activity reduction, and decreased tau hyperphosphorylation via GSK-3β/Akt pathway. Amla extract (up to 200 mg/kg; containing emblicanin A and B, punigluconin, pedunculagin, rutin, and gallic acid) improved memory and learning in chemically impaired animals, showing similar benefits in healthy animals. Dhingra et al. (2012) suggested amla's antidepressant effects and its interaction with neurotransmitters.

4. CONCLUSIONS

Amla's diverse phytochemistry, notably polyphenols, offers health benefits, particularly its potent antioxidant capabilities. These compounds directly inhibit oxidative reactions and boost endogenous antioxidants. Amla's polyphenols exhibit health-promoting effects, enhancing antioxidant status, protecting the digestive tract, and regulating glucose and insulin levels. Further research, particularly involving animals and humans, is necessary. Investigating compound bioaccessibility, interactions with gut microbiota, and integrating amla into functional foods are essential future research directions.

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CHAPTER 3

MEDICINAL AND AROMATIC PLANTS WITH QUORUM SENSING AND BIOFILM INHIBITORY EFFECTS

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INTRODUCTION

Throughout human history, the first records of medicinal and aromatic plants date back to the Mesopotamian civilization in 5000 BC (Avan, 2021). For thousands of years, human beings have used medicinal and aromatic plants to cure or prevent diseases. The history of aromatic and medicinal plants is related to the variation of civilizations and these plants play a vital role in medicine, culinary preparations, and cosmetology for several cultures such as the Middle East, China, and Greece. Seed, root, fruit, flower, root-stem, bark, tuber, woody or stem structure, herba, and leaf of these plants are dried and prepared to a certain extent. They are used in nutrition as nutritional supplements, cosmetics, body care, incense or religious ceremonies, herbal teas, flavors, condiments, various branches of industry as brighteners, and even insecticides (Alreshidi et al., 2020; Temel et al., 2018).

Türkiye has a rich flora and contains many plant species. There are approximately 11000 plant taxa and about 500 of them are used for alternative medicine (Göktaş and Gıdık, 2019). Moreover, it is one of the major countries in the trade of medicinal and aromatic plants owing to its large surface area, plant and climate diversity, geographical location, and agricultural potential (Boztas et al., 2021). Medicinal aromatic plants are mostly gathered in the Aegean, Mediterranean, Southeastern Anatolia, Marmara, and Eastern Black Sea regions in Turkey, (Göktaş & Gıdık, 2019).

The use and production of medicinal aromatic plants are increasing worldwide. In the world, between 50000-70000 plant species are used in the area of medicine. The use of plants to treat diseases varies according to the level of development of countries. In developing countries, 80% of people are treated with herbal products. In some countries in the Middle East, Asia, and Africa, this rate is as high as 95%. For developed countries, this ratio is around 49% in France, 48% in Australia, 42% in the USA, and 40-50% in Germany (Acıbuca & Budak, 2018; Göktaş & Gıdık, 2019). Today, 25% of pharmaceutical medicines are produced from these therapeutic plants (Boztas et al., 2021). The market share of aromatic and medicinal plant products is rising in relation to health awareness. The most exported medicinal and aromatic plants from Turkey are bay leaf, aniseed, cumin, ginger, and thyme. The increasing production and commercialization of natural health supplements and personal care products have created a growing industrial demand for medicinal and aromatic plants. Fixed and essential oils are utilized in the food industry, in soft drinks and confectionery, and in the cosmetics industry in perfumes, skin and hair care products, and aromatherapy (Varlı et al., 2020).

Aromatic plant parts with characteristic aromas are utilized to extract aromatherapy oils and essential oils, which are the main allelochemicals of economic value. More than 6,000 medicinal herb species have been recognized from various tropical areas in the world, while more than 1,000 of them are classified as aromatic plants. Aromatic and medicinal plants frequently cultivated and used in Turkey and around the world are as follows: *Rosa* spp. (Rose), *Dianthus caryophyllus* L. (Carnation), *Lavandula* spp. (Lavender), *Mentha piperita* L. (Mint), *Salvia officinalis* L. (Sage), *Humulus lupulus* L. (Hops), *Sesamum indicum* Linn. (Sesame), *Aloe vera* L. Burm., *Carthamus tinctorius* L. (Safflower), *Asparagus* spp. (Asparagus), *Rosmarinus officinalis* L. (*Salvia rosmarinus*) (Rosemary), *Pimpinella anisum* L. (Anise), *Coleus forskohlii* Briq (Collar flower-Leaf beauty flower), *Rauwolfia serpentina* (L.) Benth. ex Kurz (Snake root), *Cade juniper* (*Juniperus oxycedrus* L.), *Phoenician juniper* (*Juniperus phoenicea* L.), *Withania somnifera* (L.) Dunal (Winter Cherry- Poison Gooseberry-Indian Ginseng), *Chlorophytum borivilianum* Santapau & Fernandez (Musli), *Papaver somniferum* L. (Poppy) and *Ocimum sanctum* L. (Tulsi, Holy Basil) (Avan, 2021; Boudiba et al., 2021).

1. QUORUM SENSING (QS) AND BIOFILM FORMATION IN BACTERIAL VIRULENCE

Quorum Sensing (QS) is a mechanism dependent on cell density and is responsible for the production of bacterial virulence factors that play a significant role in pathogenicity and resistance. QS is regulated by gene expression and is one of the most important obstacles to overcome to combat bacteria. Bacteria release signals or autoinducers (AIs) that actulize cell-to-cell communication, and AIs have been defined as N-acyl-homoserine lactones (AHLs) and oligopeptides in Gram-negative and Gram-positive bacteria, respectively (Kiymaci et al., 2022; Wang et al., 2019).

Biofilms are sessile bacterial colonies that adhere to biotic or abiotic surfaces, which play a basic role in the survival of bacteria under adverse environmental conditions and bacterial pathogenesis (Mohammadi Pelarti et al., 2021; Kilic & Bali, 2023). Bacterial cells in biofilms differ from their planktonic analogs in gene expression and growth model, which particularly arrange the progress of biofilms under several circumstances (Awadelkareem et al., 2022).

The production of biofilm occurs from consecutive processes of adhesion and coaggregation, motility, and QS, which could be related to these chemical signals that specify the behavior of the microbial group. Therefore, it is significant to search for options that can interfere with these factors and, accordingly, obstruct the biofilm formation (Dos Santos Alves et al., 2023). Biofilm production can contain dangerous conditions in several fields such as dental, medical, agricultural, industrial, and environmental microbiology. Biofilm can occur in several sites of the human body, including the gastrointestinal tract, respiratory tract, oral cavity, and wounds, and cause several infections (Kilic &Bali, 2023).

Biofilm and QS formation are tightly dependent processes. QS process is one of the organizers of the production and dispersion of biofilm formation via small molecules that initiate biofilm phenotypes. QS can arrange the behavior of bacteria in reply to the cell volume produced by these signal molecules. and arranges the biofilm production of Gram (+) and Gram (-) by the AHLs and oligopeptides, respectively (Kilic&Bali, 2023). Moreover, the QS system is associated with antibiotic resistance, as well as bacterial proliferation in infectious tissue (Mohammadi Pelarti et al., 2021).

Excessive use of antibiotics has led to the occurrence of multi-resistant bacterial infections. The disadvantage of these antimicrobials is their selective pressure and insufficiency to treat infections that emerged by bacterial biofilms (Bali et al., 2019). QS inhibition (QSI) is considered a good strategy to control bacterial infections. In addition, according to the relationship between biofilm formation and QS activity, most anti-QS agents display anti-biofilm activities (Mohammadi Pelarti et al., 2021). QS inhibitors can target QS systems rather than killing bacterial cells, and decrease the pathogenicity, which can slow or reduce the selective pressure for growing resistance (Wang et al., 2019).

Compared to antimicrobials, plant-natural compounds are not usually related to many adverse effects, and they have a considerable inhibitory potential for infectious diseases (Bali et al., 2019). Thus, researchers look for different solutions against bacterial infections as alternative therapy modalities like the availability of active ingredients from several medicinal and aromatic plants including herbs, essential oils, and spices (Kiymaci et al., 2022).

1.1. Medicinal and Aromatic Plants Effective on Quorum Sensing and Biofilm Inhibition

Equisetum hyemale (*E. hyemale*) is a common plant found almost everywhere in the world, especially in Central and South America. Commonly, all species of *Equisetum* are known as "Cavalinha" because of the resemblance of its stem to a ponytail. The roots of *E.hyemale* are used to cure various pathologies such as eye diseases, digestive disorders, hypertension, and kidney infections. The plant also has antibacterial and antifungal properties. It contains caffeic acid derivatives and high levels of phenolic compounds. The raw extracts and fractions of *E.hyemale* also show antibiofilm activity (Dos Santos Alves et al., 2016; Dos Santos Alves et al., 2023). In the study, the anti-quorum sensing (QS) and the antibiofilm activities of a raw extract, fractions, and main compounds produced by *E. hyemale* were investigated against *Pseudomonas aeruginosa* (*P.aeruginosa*). The results showed that the crude extract and fractions hindered the biofilm production by 29- 64%, while the main compounds blocked the formation of biofilm by 67-79%. Furthermore, all compounds and extracts were found to inhibit swarming, swimming, and twitching motility of *P.aeruginosa* (Dos Santos Alves et al., 2023).

Chromobacterium violaceum (ATCC 31532) is a well-known Gram-negative bacterium with visible violacein pigment and QS regulatory system. Therefore, it is widely used for screening QS inhibitors and investigating the mechanism of QS inhibitors. N-hexanoyl-l-homoserine lactone (C6-HSL), the QS signaling molecule of the bacterium, regulated by the *cviI* gene, attaches to the transcriptional regulator to arrange biofilm production, swarm motility, and releasing of virulence factors like exopolysaccharide, and violacein (Wang et al., 2019). In the study of *E. hyemale*, the main compounds, and the extracts were found to reduce substantially violacein production, which shows an anti-QS effect. As a result, it was revealed that this herb shows biofilm inhibitory activity and interferes with QS, and the factors of biofilm formation (Dos Santos Alves et al., 2023).

Xanthomonas axonopodis pv. phaseoli (Xap) is one of the most important seed-borne destructive pathogens of beans. Xap is thought to have acquired resistance to synthetic bactericides and antibiotics. Therefore, inhibition of QS-mediated virulence factors using plant extracts is considered a good alternative for the control of plant pathogens that have acquired resistance to antibiotics and synthetic bactericides. In the study on QS inhibition, 14 different aromatic and medicinal plants were investigated against QS-mediated virulence factors of Xap. These results showed that *Thymus vulgaris, Coriandrum sativum, Syzgium aromaticum, Lepidium sativum, Brassica nigra,* and *Ruta chalepenis* will be possible candidates as anti-QS agents in hindering widespread bacterial disease of beans produced by Xap. Therefore, further research is required on the nature and mode of action of these anti-QS plant extract compounds (Belete&Bastas, 2021).

Thymus satureioides Coss., belonging to the *Lamiaceae* family, is a medicinal plant commonly known as salt thyme. It is a perennial shrub found only in the semiarid fields of the Moroccan High Atlas and AntiAtlas. This plant is traditionally used to treat various diseases such as fever, bronchitis, hypertension, diabetes, skin and circulatory disorders, immune system problems, pain perception, influenza, and pharyngitis. Furthermore, the pharmacological features of *T. satureioides* essential oils and extracts include their anticancer, antimicrobial, antidiabetic, anti-inflammatory, hypolipidemic, and insecticidal effects. The study on the anti-QS effect of *T. satureioides* extract showed that the extract decreased biofilm production, swimming motility, exopolysaccharide, and extracellular protein production of *Pseudomonas aeruginosa*. This result demonstrated that the extract had anti-QS properties. The plant and its compounds are considered hopeful alternatives for use in the improvement of novel medicines and food support (Mahdi et al., 2023).

Cyprus is in the northeastern corner of the Mediterranean Sea. Due to both climatic conditions and soil, there is a great diversity of plant chemotypes. More than 650 medicinal plants have been specified in Cyprus and the flora of Cyprus is rich in endemic taxa. In the study on the QS inhibitory effect, the aromatic plants *of Aloysia citriodora, Calendula officinalis, Rosmarinus officinalis, Salvia officinalis, Lavendula spp., Origanum vulgare subsp. Hirtum*, *Melissa officinalis,* and *Sideritis cypria* were investigated and the anti-QS properties of the ethanolic extracts were studied. Firstly, the QS inhibitory effects of the extracts were assessed using *Vibrio harveyi* BB170 which is a reported strain on autoinducer 2 (AI-2) signaling activity. Later, the activity of the extracts on QS-mediated processes including swimming and swarming motilities and biofilm production of *Escherichia coli* MG1655 were evaluated. In the results, the extracts of *Rosmarinus officinalis*, *Salvia officinalis*, and *Origanum vulgare* subsp. Hirtum were found to be the most effective AI-2 signaling inhibitors while the other extracts showed low to moderate QS inhibitory effects. The AI-2 molecule is a globally interspecies signaling molecule. Thus obstruction of AI-2 production could be a prospective strategy to check the pathogenicity of bacteria. Furthermore, the biofilm production (>60%), swarming and, swimming movements of *E. coli* MG1655 also were hindered via the three ethanolic extracts. The study suggests that plants from Cyprus flora may serve as new QS inhibitory agents to cure infectious diseases induced by antibiotic-resistant pathogens. Furthermore, it was indicated that these three extracts may be accepted for the identification and forward optimization of new QS inhibitory agents for biofilm treatment (Panayi et al., 2022).

Multidrug resistance is a major clinical challenge in pathogenic bacteria and QS, which regulates virulence and is an encouraging key medicine target for the prevention of multidrug resistance infections. In the study of multidrug resistance bacteria, anti-QS effects of methanolic extract of 18 medicinal plants were performed against *Chromobacterium violaceum* 12472. The most effective extract of *Acacia nilotica* (ethyl acetate fraction) was tested against QS and biofilm formation of *Serretia marcescens* MTCC 97 and *Pseudomonas aeruginosa* PAO1. In the results of the study, many plants were found to have QS inhibitory potential. In particular, the extract of *A. nilotica* was detected QS and biofilm inhibitory effects on *S. marcescens* MTCC 97, *C. violaceum* 12472, and *P. aeruginosa* PAO1. Thus, many extracts of medicinal plants could be used as promising anti-QS agents, which reduce the virulence factors of test strains (Samreen et al., 2022). In another study, the anti-QS activity of 25 plant extracts was performed using *Chromobacterium violaceum* MCC 2290 (ATCC® 12472™) known as wild type bioreporter bacterial strain. The results showed that the acetone: water (1:1) crude extracts of *Terminalia chebula* Retz., *Terminalia bellirica* Roxb., and *Punica granatum* L. exhibited QS inhibition in different concentrations. The extract of *P. granatum* L. exhibited the most effective QS inhibitory violacein inhibition of 41.92%. Furthermore, all the extracts were detected to exhibit QS inhibition at a concentration of ≥ 0.075 mg/ml. For this study, the phytochemical contents of crude extracts are recommended to be determined for a better understanding of their pharmacological activities (Mehta &Jadeja, 2019).

Castanea sativa (*C. sativa*), belonging to the *Fagaceae* family, is a plant known as sweet chestnut. It has been utilized in folk drugs from the past to the present to cure many diseases such as asthma, diarrhea, bronchitis, colds, back pain, heart, and rheumatism. In the study of flower extracts of *C. sativa,* anti-QS properties of the extracts were performed against indicator strains, *Chromobacterium violaceum* 35352, *C. violaceum* CV026, *C. violaceum* ATCC 12472, and *C. violaceum* VIR07. *Pseudomonas aeruginosa* PAO1 strain was used to detect the inhibition of biofilm and swarming motility. In the results, methanol extract of *C. sativa* flowers was found to display QS inhibitory effects via hindering the biofilm formation, violacein production, and swarming motility. QS inhibitory agents isolated from plants are known to have great potential in combating multi-resistant pathogens due to their drug-like functions. Thus, in the present study, it was suggested that the flower extracts of *C. sativa* could be used as QS inhibitory agents in the development of new anti-pathogenic agents. However, further studies are needed to highlight this aspect of extracts and their active ingredients (Ekşi et al., 2020).

Eruca sativa Miller (*E. sativa*), belonging to the *Brassicaceae* family and commonly known as the 'Rocket plant', is a prominent aromatic plant widely used in diet and medicines and it is a favored greens salad in many countries. It is used in traditional medicine to fight against eye infections and to increase sperm production, fertility, kidney activity, and the digestive process. It has analgesic, antimicrobial, anti-inflammatory, antioxidant, anticancer, anti-diabetic, anti-genotoxic, anti-hyperuricaemic, anti-hyperlipidemic, and anti-acne properties. Raw extract of *E. sativa* was tested against bacteria in food. It was found that the extract has antibiofilm effect against *Escherichia coli* (MTCC) 9537, *Salmonella enterica serovar* typhi (MTCC 8767), *Pseudomonas aeruginosa* (MTCC 741), and *Staphylococcus aureus* (MTCC 96) and showed the biofilm inhibition from 58.68% to 73.45% against all tested bacteria. The extract was also detected to decrease cell viability and EPS amount in the biofilm matrix, ranging from 59.73–82.77%. Furthermore, the extract caused significant disruptions in the biofilm structure of all bacteria, which was visualized by scanning electron microscopy (Awadelkareem et al., 2022).

From the family *Liliaceae*, the genus *Allium* is one of the largest monocotyledons with 800 to 900 species. *Allium* species are one of the most common plants in the world and have been a significant value in nourishment, therapy, and economics for a long time. Besides their dietary importance, *Allium* plants frequently have a particular position in traditional and complementary therapy around the world. Otherwise, *Allium colchicifolium* (*A. colchicifolium*) is one of the indigenous *Allium* species in western Iran. The leaves of *A. colchicifolium* (synonyms: *A. straussii* and *A. haussknechtii*) are consumed as a salad and side dish, and cooked as a local dish. It is also used in folk medicine as an anti-infective, antirheumatoid, and antilipidemic. Five flavonoids isolated and purified from *A. colchicifolium* leaves, which are morin, quercetin 3-O-glucoside, quercetin, isorhamnetin, and isorhamnetin-3-O-glucoside were investigated and found that all isolated flavonoids displayed antibiofilm effect. Additionally, morin and quercetin 3-O-glucoside were found to exhibit the highest antibiofilm effects on *Pseudomonas mirabilis* and *Staphylococcus aureus*, respectively (Majnooni et al., 2023).

Origanum species from the *Lamiaceae* family is a genus of the most widely utilized medicinal herbs. It has been commonly used in folk medicine for thousands of years in the treatment of various disorders, in cosmetics, and as a spice. *Origanum* species have been broadly utilized as an analgesic, antimicrobial, carminative, stimulant, astringent expectorant, antitussive, antiseptic agents, sedative, anthelmintic, antispasmodic, diaphoretic, antiparasitic, and tonic in Turkish folk medicine. They have also been used to treat headache, toothache, abdominal ache, menstrual disorders, diabetes, tachycardia, hypertension, itching, convulsive coughs, dizziness, hypercholesterolemia, respiratory tract and gastrointestinal diseases. The study on the antibiofilm activity of the water and methanol extracts of *Origanum haussknechtii* was investigated on *Pseudomonas aeruginosa*. In the results, only the methanol extract was found to be effective in the biofilm formation of *P. aeruginosa* with 80.53% inhibition. The methanol extract was also detected to hinder the biofilm formation of *E. coli* (41.33±1.53%) and *Staphylococcus aureus* (77.33±1.15%). *O. haussknechtii* can be utilized for application as new bioactive substances in cosmetics and pharmaceutical crude materials as well as dietary supplements (Ayaz et al., 2021).

Laurus nobilis L., belonging to the *Lauraceae* family, is an aromatic evergreen tree utilized in drugs, nutrition, and cosmetics. It is usually known as bay laurel and is one of the most extensively utilized spices in many countries. In the nutrition industry, it is used to flavor soups, fish, meat products, pickles, stews, and sausage sauce. It plays an improtant role in integrative medicine to cure migraines, earaches, diabetes, indigestion, sprains, rheumatism, and dermatitis. It has also antibacterial, anti-ulcerogenic, anticonvulsant, antimutagenic, antifungal, neuroprotective, antioxidant, analgesic, anticholinergic, antiviral, immune-modulating and wound healing properties. In the study of *Laurus nobilis* extracts, antibiofilm, and anti-QS activities were investigated against the Gram (+) and Gram (−) bacterial virulence. The results of this research showed that all extracts at 100 µg/mL concentration hindered to some degree the biofilm formation (until 76% of Gram-positive and 40% of Gram-negative). Chloroform and hexane extracts were found to have a biofilm inhibitory effect on *Staphylococcus aureus*. These extracts were also detected to display QS inhibitory effects on *C. violaceum* and to prevent elastase activity, biofilm formation, pyocyanin production, and swarming motility of *Pseudomonas aeruginosa*. This study showed Laurel extracts target the biofilm formation and the virulence of Gram (-) and Gram (+) bacteria, which makes them a safe alternative for controlling food spoilage and/or contamination and infectious diseases (Molina et al. 2020).

Ocimum basilicum Linn. and *Cinnamomum zeylanicum* Blume (*C. zeylanicum*) are edible and medicinal plants utilized by many cultures. *O. basilicum* Linn., known as sweet Basil, belongs to the *Lamiaceae* family and is related to the fields of pharmacology, food, cosmetics, and agriculture. *O.*

basilicum is traditionally used for the treatment of diabetes, cardiovascular disorders, cancer, diarrhea, constipation, worms, headaches, coughs, digestive disorders, kidney malfunction, warts, neuro-degenerated disorders, and menstrual cramps. *C. zeylanicum*, belonging to *Lauraceae* family, has also been widely used as a therapeutic agent and food spice in different cultures for a long time. It is utilized as a cure for diabetes, acne, urinary tract and respiratory illnesses, and gynecological and digestive troubles. In the study on the extracts of these plants, the inhibition of violacein synthesis in *C. violaceum* (CV12472) and QS formation of *C.violaceum* (CV026) were evaluated. The study results showed that both plant extracts could hinder the violacein production and QS formation of these biosensor strains. The extracts were also found to block signal reception and signal production in QS-related bacterial processes, which indicates good anti-quorum sensing activity. Pathogenic bacteria utilize QS-related properties to improve resistance and violence of infections. Therefore, these extracts were detected to be suitable for coping with microbial resistance, probably (Tamfu et al., 2021).

Teucrium polium L. (*T. polium*), Saudi Arabian folk medicine, is used to fight cold and fever, as well as intestinal and stomach troubles. *T. polium* is also considered a significant herb in the prescriptions of folk medicine. It has been advised for many years as a medication for its anti-inflammatory, antioxidant, anti-spasmodic, and anti-diabetic effects. In the study of *T. polium* extract activity, QS inhibition tests were performed using *C. violaceum* (ATCC 12472 and CV026) and *P. aeruginosa* PAO1. The findings highlighted that the extract blocked the swarming and swimming capacities and the movement of *P. aeruginosa* PAO1, decreasing its virulence (Alreshidi et al., 2020).

Citrus sinensis, *Hypericum perforatum*, and *Syringa vulgaris* are important medicinal plants that have been determined to be effective on bacterial QS-mediated virulance. *Citrus sinensis* from the *Rutaceae* family is usually called sweet orange, which is used in traditional drugs for several diseases. It exhibits also the effects of antioxidant, antimicrobial, antiproliferative, relaxant, sedative, anti-obesity, antiosteoporotic, hypocholesterolemic, and anxiolytic. *Hypericum perforatum*, which belongs to the family of *Hypericaceae*, is traditionally used in medicinal treatments for disorders like depression, minor burns, and anxiety. This plant has antimicrobial, anti-tumoral, antiviral, and antidepressant, and neuroprotective activities. *Syringa vulgaris*, also known as common lilac, belongs to the *Oleaceae* family and is broadly utilized for medicinal objectives including antioxidant, anti-inflammatory, antipyretic, and antinociceptive effects. In the study of these medicinal herbs, the ethanol:water extractions of these plants assisted by ultrasound were investigated by preparing their phenolic extracts. The results of this study revealed that the plant extracts showed anti-QS effects including the inhibition of violacein pigment production and swarming motility. The extracts were also detected to disrupt the bacterial signal molecules which diffuse all over the colony and control swarming motility (Tamfu et al., 2022).

Medicinal plants are also of great importance in the prevention of urinary tract illnesses which is one of the most widespread bacterial infections worldwide. *Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Serratia marcescens* are Gram (-) pathogens that generate drug-resistant urinary tract infections that are more strong and life-threatening owing to their biofilm-forming properties. Phytochemicals originating from desert medicinal herbs play a crucial role in preventing the biofilm growth of these bacteria. In a review study, the desert medicinal herbs with bioactive phytochemicals against uropathogens produced biofilm were reported as *Corbichonia decumbens, Commiphora wightii, Abutilon indicum, Tribulus terrestris, Aloe vera, Aerva javanica, Citrullus colocynthis, Amaranthus tricolor, Boerhaavia diffusa* and *Asparagus racemosus.* Identification of desert phytochemicals hindering the bacterial communication systems and playing as QS inhibitors are required to inhibit the metabolic activities and biofilm formation of these uropathogens (Singh et al., 2023).

2. CONCLUSION

Quorum sensing (QS)-mediated virulence features like bacterial biofilm formation, violacein pigment production, and microbial motility can indicate the bacterial resistance and severity of infections. Therefore, inhibition of the QS mechanism by disrupting signaling molecules within bacterial communication to eliminate microbial resistance, and to inhibit the production of violacein pigment in QS biosensor strains could be promising strategies to control the spread of infections that cause poor prognosis. Frequently use of conventional antibiotics increases bacterial resistance. Inhibiting the communication network between bacteria without killing them can be effective in preventing infections. Thus, substances that can inhibit bacterial QS and biofilm formation are alternative solutions that can prevent the development of multiple resistance. The use of natural compounds derived from medicinal and aromatic plants against QS production is an approach that is becoming more attractive in terms of the possibility of developing new drugs to combat antibiotic-resistant pathogens.

In this chapter, current studies on the QS and biofilm inhibition potentials of widely used medicinal and aromatic plants are mentioned. Medicinal and aromatic plants are an important value to our country and there is a need to increase the studies on the bacterial QS and biofilm inhibition potential of extracts and phytochemical compounds from these plants and detailed pharmacological, toxicological, molecular, and clinical studies.

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CHAPTER 4

PLANT EXTRACTS AND OTHER LOCAL (ETHNO VETERINARY) TREATMENTS

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INTRODUCTION

The application of plant extracts to livestock to repel or kill ectoparasites is widespread in the developing world. The idea of cultivating plants and low-cost extraction of active compounds as a local industry in developing countries has considerable appeal. There seems to be a prevailing view that plant extracts or botanicals are safer and cheaper than synthetic products. However, issues of safety of the crude extracts to humans, livestock, and the quality of produce from treated livestock should be addressed, and the economics of local production must be closely considered. Many botanicals would likely be more expensive to produce than existing organ phosphorous, synthetic pyrethroid products, and amitraz. It is clear from a brief examination of the literature that many botanical products can kill ticks or inhibit oviposition (Habeeb et al., 2010). Chabra and Saxena (1998) briefly reviewed the plants that effectively control ticks or mites in Indian traditional medicine. Twenty-one plants were shown or believed to be of some benefit. The following examination of publications relating to the homicidal effects of plant extracts confirms that many plant extracts can kill ticks in vitro. Most studies are in vitro dose mortality bioassays, most of which are based on the following approach. Firstly, extracts are prepared by hydro distillation, by combination with alcohols, or by pressing various parts of the plant. The extracts are diluted with water, oil, or alcohol, usually in 50 percent serial dilutions. A variable number of ticks are immersed in the solution, or small quantities of the solution are applied to the cuticle. The proportion of dead ticks or those failing to produce eggs is determined, and the average mortality is reported for each concentration. Probit analysis is rarely undertaken, and LC50s and LC99s are rarely calculated. Fewer researchers attempted in vivo bioassays in pen or field. With a few exceptions, where pen and field studies were conducted, the description of the procedures would not enable the studies to be duplicated (Quadros et al., 2020). Details about infestation rates prior to treatment, preparation of the test solutions, method of application, environmental conditions at the time of application, other treatments that test animals had been exposed to, and the resistance profile of ticks are rarely provided in sufficient detail. The concentrations that are used appear to be driven by convenience and are often restricted to less than a five-fold difference between the highest and lowest. Most papers do not report the extract yield from the original plant material, so it is impossible to determine the amount of plant material required to undertake a pen or field study or to estimate the economic feasibility of the plant. The oil vehicle in one in vivo study caused mortalities that were comparable with the extract being tested, but the obvious question as to why you would bother adulterating the oil with the extract was not addressed (De Lillo et al., 2010). None of the papers provided a serious discussion of the possible economic feasibility of the plant extract under consideration. Toxicity studies were rare among the papers examined. The one of the only repeatable and thorough examinations of possible toxicoses resulting from the application of plant extracts. Many researchers seem to believe that being of botanical origin guarantees safety to animals, humans, and the environment – obviously not true (Gallego et al., 2012). The questions that need to be answered before any plant extract can be recommended for inclusion in an integrated control program for any locale are:

i. How can a product be formulated from the raw materials?

ii. How effective is the product against the local species of ticks?

iii. What will the product cost per treatment?

iv. Is the product safe for animals and humans in contact with it?

v. Is the product safe for the environment?

vi. Does the product have any unacceptable residues or cause any undesirable effects in animal products?

Unfortunately, although acaricide effects have been demonstrated for many plant extracts, none of them has been studied to the point where the questions above can be answered. Plants that have been evaluated and shown some acaricidal properties include *Azadirachta indica*, *Ocimum suave*, *Gynandropsis gynandra*, *Cleome hirta*, *Gutierrezia* spp., *Margaritaria discoidea*, *Pimenta dioica*, custard seed oil, *Commiphora erythraea*, *Artocarpus altilis*, *Stylosanthes scabra*, *Tamarindus indicus*, peel oil of *Citrus* spp., and *Stemona collinsae*. Each of these is discussed in alphabetical order below. The list is unlikely to be comprehensive.

1. NEEM (*Azadirachta indica* A. Juss.)

The neem tree originated in Asia and grew well in tropical and subtropical areas of the world, in areas of marginal fertility and low to moderate rainfall (400 to 800 mm per annum). It is commonly included in re-forestation programs in the developing world. Oil from seeds of the neem tree contains azadirachtin as a principal biologically active component, which has been shown to have inhibitory effects on vitellogenin during the oogenesis of arthropods (Alzohairy and Medicine, 2016). Neem also includes meliantriol, salannin, and the triterpenoids nimocinolide and isonimocinolide. Several studies have been conducted on the effect of neem extracts on cattle ticks. Treated and untreated cattle were grazed together on naturally infested pastures, and the dominant tick species were *Amblyomma hebraeum, Rhipicephalus evertsi*, *Hyalomma truncatum* and *Boophilus decoloratus*. Over the whole year, the average number of ticks of all species on control animals was 37.5, compared with 19.75 in the neem-treated group, a statistically significant difference. *Boophilus microplus*, using a 5 percent soapy aqueous extract on naturally infested animals treated every 21 d showed similar efficacy to an amitraz-based commercial acaricide in two field trials (Deng et al., 2012). They also demonstrated high efficacy (100 percent control of reproduction) *in vitro*, when using an ether extract, while alcohol extracts resulted in 70 percent reduction of reproduction by the tick. Toxicity studies on rabbits (ocular instillation, dermal sensitivity, intradermal inoculation, entire immersion) did not cause any adverse effects. Results from studies in India were not as promising. Although the methodology is incompletely described, their work indicated that neem oil, of unspecified derivation, caused reductions of about 70 percent in vivo, in populations of *Hyalomma anatolicum anatolicum*, *Boophilus microplus* and *Rhipicephalus haemaphysaloides*. *In vitro* studies showed that neem oil inhibited oviposition at all, although the methodology is not described in this paper. Ethanol extracts of neem were found to be effective at inhibiting oviposition. Ethanol extracts of varying concentration were applied individually to engorged *B. microplus* females. Probit analysis determined that the concentration at which oviposition was inhibited in 50 percent of females was 0.54 µg. It was noted that the oocytes of neem-treated ticks were lighter colored and smaller than those of the control ticks, that a large proportion of egg masses were deformed, and that eclosion failed in 80 percent of the eggs that were produced by treated ticks at the concentration that caused 50 percent inhibition of oviposition. Further, there were alterations in the proportions of proteins and methyl ester derivatives. Protein concentrations were increased with treatment, while methyl ester derivatives were inhibited. The studies described above indicate that extracts of the neem tree have the potential for the control of *B. microplus* (Patoliya et al., 2022). There remains a need for dose-mortality studies conducted on animals in controlled environments to determine the most suitable concentration for application to cattle in the field and the duration of repellent effects. Further, the productivity of neem trees in terms that allow for the estimation of the cost-effectiveness of its extracts for controlling ticks has not been demonstrated.

2. CALOTROPE (*Calotropis procera*), AGANONERION (*Aganonerion polymorphism*), DILL (*Anethem graveolens*)

It was studied the acaricidal effects of combinations of two crude ethanol extracts of 34 plants to identify possible synergistic effects against *B. microplus*. Maximum *in vitro* effects 24 h after exposure were noted in the combination of *Calotropis procera* with *Aganonerion polymorphum* (71 percent mortality) and in the combination of *A. polymorphum* with *Anethem graveolens* (68 percent mortality). It was claimed that the results of these combinations represent synergistic effects because they are much higher than those obtained from each non-combined crude extract (all < 10 percent). This work represents a preliminary screening study and requires dose-response studies, both in vivo and in vitro as well as toxicity and feasibility studies before these combinations can be considered realistic options for application to cattle (Khan et al., 2019).

3. *Capsicum* spp., *Euphorbia obovalifolia, Ficus brachypoda, Solanum incanum*

The Ethnoveterinary methods of tick control practiced in western Ethiopia have been examined by a survey of farmers, followed by *in vitro* and *in vivo* testing of treatments that appeared to have potential (Regassa, 2000). Commonly used treatments included *Capsicum* spp. commercial spice mixed with butter fat, the juice of crushed leaves and bark of *Calpurnea aurea*, crushed seeds of *Lepidium sativum* mixed with fresh cattle faeces, juice of crushed leaves of *Vernonia amygdalina*, the latex of *Euphorbia obovalifolia*, fruit juice of *Solanum incanum*, juice of crushed leaves of *Phytolaca* *dodecandra* and the latex of *Ficus brachypoda*. of these, *Capsicum* spp., *E. obovalifolia*, *S. incanum* and *F. brachypoda* were the more effective treatments when tested in vitro, causing 100, 92, 42 and 83 percent mortality of *B. decoloratus* respectively after 20 minutes of exposure (Flamini et al. 2003). *In vivo* tests were conducted using a small number of animals infested with *A. variegatum* and *A. cohaerens.* Results appear promising for *E. obovalifolia* and *F. brachypoda*, although the small number of animals and ticks and the nature of the applications involved in these trials limit the conclusions that can be drawn from them. A possible problem with *E. obovalifolia* is that its application resulted in localized hair loss and is known to irritate eyes and skin. *Citrus s*pp. peel oils Although d-limonene, a major component of citrus peel, has been shown to have insecticidal properties (Chhabra et al. 2014). Oil was obtained by mechanical compression of the peel of five species: *Citrus suncris*, *C. maxima*, *C. reticulata*, *C. hystrix* and *C. sinensis*. Of these species, *C. maxima* and *C. reticulata* had the strongest acaricidal effect, killing more than 95 percent of ticks in a 10 percent dilution. The authors propose that citrus peel oils could be extracted from waste fruit and sprayed directly onto cattle for tick control. *Cleome hirta* is a shrub that is native to southern Africa and there is only a single recent reference to its use as a tick repellent, although it is reported to be used for treatment of stomach aches in eastern Africa. Climbing repellency tests using *R. appendiculatus* (stage not stated) were conducted and it was shown that the essential oil, extracted by hydrodistillation and used at four logarithmic concentrations, achieved between 90 percent (0.1 percent) and 18 percent (0.0001 percent) repellency. This was equivalent to DEET, which was used as a reference at the higher two concentrations. The identified constituents of the *C. hirta* essential oil were (+)-cedrol, phytol and *n*-octacosane, each of which achieved lower levels of repellency when used alone (Abdisa et al., 2017). The use of extracts from *C. hirta* in integrated control programs cannot be recommended until in vivo dose-response trials, toxicity and feasibility studies have been completed.

4. ETHIOPIAN MYRRH (*Commiphora erythraea*)

Commiphora erythraea is a small buseracean tree that grows in Eritrea, Somalia, Ethiopia, and parts of the Arabian Peninsula. The gum or latex of the tree has been collected for hundreds of years and used as a component of incenses, balms, and Chinese medicines (Temba et al., 2017). Furano-sesquiterpenoids extracted from its gum have been shown to have acaricide effects. Hexane extracts were larvacidal against *A. americanum*, the lone star tick, and *Dermacentor variabilis*, the American dog tick. Against *A. americanum*, 96 percent mortality was obtained with a concentration of 0.02 mg/cm 2 of extract on filter paper, while 0.16 mg/cm 2 was required to kill 80 percent of *D. variabilis*. The extract also had a moderate repellent effect against both species. The species of ticks against which this plant extract was evaluated are not significant problems for livestock producers in the developing world, and there are clear differences among the species evaluated in their response. However, bioassays using ticks of economic importance to livestock producers in the developing world appear to be warranted (Swai et al. 2017). Given the high cost of gum from this plant, the feasibility of production of sufficient quantities of plant materials should be considered first.

5. BROOM SNAKEWEED (*Gutierrezia sarothrae*) AND SNAKEWEED (*Gutierrezia microcephala*) BROOM SNAKEWEED *(Gutierrezia sarothrae)* AND THREADLEAF SNAKEWEED *(Gutierrezia microcephala)*

These perennial plants infest grazing land in western North America and have been shown to contain saponins, flavonoids and terpenoids. The small amount of the normally unpalatable weed that herbivores ingests when preferred feeds are unavailable might be toxic to ticks, and that extracts from the ticks might have repellent effects. They allowed nymphal lone star ticks 1 (*Amblyomma americanum*) to feed on rabbits that had been fed on snakeweed at 5 percent and 10 percent or a control diet and found that engorgement success was about one third less among ticks on snakeweed-fed rabbits. Snakeweed extracts also demonstrate a repellent effect when applied to the skin. However, it was concluded that ingesting snakeweed was not a viable means of controlling ticks because it also compromised feed intake and weight gain. The cause of the repellent effect of extracts of snakeweed is uncertain but likely merits further investigation. It appears that snakeweed might have acaricidal and repellent effects. It cannot be recommended for inclusion in IPM programs until in vitro and in vivo studies have confirmed its efficacy, and toxicity studies indicate that it is safe for application to animals and humans (Habeeb et al. 2010). This work is unlikely to be undertaken, given the current distribution of the weed and its known toxicity by ingestion.

6. AFRICAN SPIDERFLOWER (*Gynandropsis gynandra*)

Gynandropsis gynandra is an East African shrub of the Capparidaceae that has been proposed as an anti-tick pasture plant and is a common Indian treatment for arthritis, possibly effective because of inhibition of phospholipase A2 activity. Methanol extracts of *G. gynandra* have also been shown to be effective against the following helminth parasites *in vitro*: *Fasciola giganticum*, *Taenia solium* and *Pheretima posthuma*. As described in the previous section on pastures with repellent or lethal effects, *G. gynandra* has clear repellent and acaricidal effects when planted in pastures (Lwande et al. 1999). Oil extracts of the plant have also been tested. *G. gynandra* found that methyl isothiocyanate, known to be toxic to arthropods was a major component. It is identified and tested that repellent effects of 28 compounds in the oil of the plant against *R. appendiculatus* ticks, although the stage used and details about the procedure are not specified in the paper. They found that the repellency of the oil was comparable with that of N,N-diethyl-toluamide (DEET) when used at a high dosage. When fractionated, the most repellent compounds were m-cymeme, nonanal, 1- *α*-terpeneol, *α*-cyclocitral, *β*-cyclocitral, nerol, trans-geraniol, carvacrol, *α*-ionone, transgeranyl acetone, nerolidol and cedrene. All these products had similar repellency to DEET. It appears that the essential oils of *G. gynandra* have repellent effects and that when planted in pastures, these effects are also noteworthy. In order to progress to an effective product to aid in the control of ticks, *in vivo* dose-response studies are required to determine effective concentrations; toxicity studies are needed given the potential toxicity of some of the plant's extracts; and the cost-effectiveness of extraction and application should be determined (Fouché et al. 2017).

7. KUPETABA: TOBACCO LEAVES AND MAGADI SODA

Kupetaba is "a mixture of dried tobacco leaves and M agadi soda" and is available in markets throughout East, West, and Central Africa. Kupetaba in vitro and in vivo against *Rhipicephalus appendiculatus* ticks found moderate in vitro and in vivo effects. Kupetaba killed all stages of the tick, prevented the completion of feeding, and suppressed oviposition. The saturated solution had a slight residual effect, and the authors recommend a regime of alternate application of kupetaba and hand de-ticking. Dose-response studies were not conducted, nor was the concentration of any likely active components quantified, apart from the statement that a saturated solution was prepared as stock solution. It is unclear what Magadi soda is, where it is obtained, and how variable its composition is (Magano et al., 2011). Questions, therefore, arise about the consistency of formulations of Kupetaba and the optimal dosage that would need to be addressed before recommending its inclusion in an integrated control program.

8. *Margaritaria discoidea*

Margaritaria discoidea is a termite-resistant Euphorbiaceae tree growing to about 10 m along riverbanks in Africa. Its wood is used as a perfume and is burnt as a mosquito and snake repellent. Aqueous extracts of bark and hexane extracts of wood were prepared and mortality studies were undertaken on *A. variegatum* and *R. appendiculatus* ticks (Habeeb et al., 2010). They conducted in vitro repellency and dose mortality studies and in vivo controlled studies using rabbits and cattle. Residual activity was also examined. Water extracts of bark were variably effective against nymphs of both species, mortalities ranging from 72 percent (*R. appendiculatus* nymphs) and 58 percent (*A. variegatum* nymphs) at 25 percent concentrations to 96 percent (*R. appendiculatus* nymphs) and 99 percent (A. variegatum nymphs) at 100 percent concentrations of the aqueous extract. Adult *R. appendiculatus* ticks were less affected, with 25 percent and 100 percent aqueous solutions resulting in 29 percent and 70 percent mortality respectively. Adults of A. variegatum were not affected at all by any concentration. Hexane-oil extracts from the wood appeared to have a more substantial acaricidal effect in vitro than the aqueous bark extracts, with almost all concentrations resulting in 100 percent mortality. However, the effects of the oil base on A. variegatum (90 percent mortality in the control group) undermine any interpretation of the results. The same problem of high control mortalities is evident in the rabbits' mortality studies. In vitro, repellency studies indicated a strong effect against *R. appendiculatus* adults and nymphs, but none against *A. variegatum*. In zebu cattle that were naturally infested with *R. appendiculatus*, a 50 percent hexane extract of *M. discoidea* in corn oil they resulted in 90 and 100 percent reductions in ticks at days one and two after application, while control animals experienced a 10 to 15 percent reduction in the number of ticks (Ezegbe et al., 2021). In the field, there was no extended protective period, ticks beginning to increase after 2 d. However, the trials on rabbit ears indicated some protection for 4 d. *Margaritaria discoidea* extracts were ineffective against *A. variegatum*, inducing a maximum of 50 percent mortality. *M. discoidea* might have some value for the control of ticks however the lower efficacy against stages of *A. variegatum* could be problematic. Furthermore, it is clear from the high control mortalities that the dose response studies should be repeated using hexane extracts with a broader range of potential vehicles. More complete bioassays should be undertaken before further studies in the field (pen trials, toxicity studies and feasibility studies) are undertaken.

9. *Ocimum suave* Willd.

Ocimum suave is a shrub commonly found in the upland areas of East Africa, and it has been used for various medicinal purposes, including as an insect repellent. Dose mortality studies using oil extracted from the plant by steam distillation were conducted on the larvae of *R. appendiculatus* and demonstrated a high level of effectiveness. The LC_{50} for the oil was 0.024 percent. The oil was also repellent *in vitro*, and *in vivo* studies showed that the oil could protect rabbits from larval infestation for 5 days. Unfortunately, these promising results were not confirmed by field studies using cattle, where three applications per week of a 20 percent solution reduced the number of ticks by 68 percent (Mvumi et al., 2021). It is uncertain why there is such a difference between the laboratory and field efficacy of the oil, but it may be related to the application method.

10. PIMENTO (*Pimenta dioica*)

Pimenta dioica is a tropical tree whose berry is dried and ground to produce allspice, containing the phenyl propanoids eugenol, methyl eugenol and caryophyllene. Bioassays using engorged, adult *B. microplus* ticks indicated that applying the leaf hexane extract at a rate of 4.0 mg/g of ticks resulted in 10 percent mortality and 24 percent inhibition of oviposition. This result was more or less by previous work in which 5.0 mg/g application resulted in 17 percent mortality and 24 percent inhibition of oviposition. The maximum inhibition of oviposition was 47.2 percent, and this was achieved with hexane extract from the berry at 4.0 mg/g ticks. Essential oil of the berry was far more effective, resulting in 100 percent mortality over 96 h, when applied at 4 mg/g ticks. Similar activity was obtained with eugenol (Gomes da Rocha Voris et al., 2018). The authors compared the activity of the essential oil favorably with the same concentrations of some organophosphorus compounds, carbaryl, and the juvenile hormone analogue farnesyl methyl ether. However, ticks were collected from an abattoir and were not of a known susceptible strain, and it is difficult to determine how the commercial acaricides were formulated for the bioassay from the materials and methods. Based on the work described, it is difficult to know how valuable this plant might be for controlling ticks (Chhabra et al., 2014). More rigorous dose-response bioassays are required before any further studies can be recommended.

11. *Solanum dasyphyllum* Schumach. & Thonn., *Neorautanenia mitis*

A survey of the potential acaricidal effect of 42 medicinal plants from Rwanda found that 13 showed some acaricidal effect against *R. appendiculatus*. Of these, petroleum ether fractions of *Solanum dasyphyllum* fruits and *Neorautanenia mitis's* roots completely inhibited oviposition. No in vivo studies were conducted, and no suggestions were made about the potential effects of these extracts on humans or livestock.

12. *Stemona collinsae*

Plants of the Stemonaceae are the source of the complex family of *Stemona collinsae* alkaloids and have been used in traditional Asian medicine as anthelmintics and to treat respiratory diseases. They are also known to have anti-fungal effects. Extracts of the leaves and roots of *S. collinsae* have high insecticidal and anti-feeding activity against *Spodoptera littoralis*. The insecticidal effects were attributed to pyrrolo [1,2-a] azepine alkaloids, particularly didehydrosternofoline (asparagamine A) (Brem et al., 2002). Bioassays using *S. collinsae* root extracts and *B. microplus* immature and adult forms were conducted. Fifty percent concentrations of *S. collinsae* caused 100 percent mortality in vitro in “seed ticks” of *B. microplus*. Mortality fell to 76 percent when 20 percent concentrations were used. In vivo results were almost identical, ranging from 76 percent mortality at 20 percent concentration to 100 percent mortality when the 50 percent concentration was used. A mortality rate of 93 percent was seen in engorged (Sakulpanich et al. 2023).

13. *Stylosanthes scabra*

There is a single report on the efficacy of methanol extracts of the leaves of *S. scabra* against *B. microplus*, *Haemaphysalis intermedia* and Rhipicephalus sanguineus. It was realized up to 35, 20 and 41 percent mortality against *B. microplus*, *H. intermedia* and *R. sanguineus* respectively. The dilutions that were used in their study are very close (0.1 up to 0.6 percent) and it is impossible to say whether more useful rates of mortality could be achieved with higher concentrations, however extracts from the plant do not look promising as acaricides (Patra et al., 2022).

14. TAMARIND (*Tamarindus indicus*)

The effect of aqueous and ethanol extractions of tamarind fruits, as well as of their chief organic acids (oxalic, malic, succinic, citric and tartaric acids) on engorged, adult *B. microplus*. Maximum mortality rates achieved by the fruit extracts at 48 h ranged from 70 to 89 percent (Adenubi et al., 2016). Patchy haemorrhagic swelling of the tick cuticle was noted in all treatments 15 minutes after application. Preparations of 0.5 and 1.0 percent oxalic acid resulted in 56 and 62 percent mortality respectively after 24 h and resulted in similar cuticular changes. One question arising from this work is whether the application of such extracts is likely to cause dermatitis and keratitis in treated animals. Otherwise, more complete bioassays and analysis would be required to estimate effective concentrations for pen trials and the economic feasibility of directing a commercially valuable fruit to control of ticks should be considered (Shahrajabian et al. 2021).

15. *Tephrosia vogelii*

It is a botanical insecticide that has been extracted from the roots of *Derris* spp., *Lonchocarpus* spp., and *Tephrosia* spp., and has been used for the control of insects, spiders, mites, ticks and fish 2002). Using *T. vogelii* aqueous root extracts (10 percent) to control *B. decoloratus* in Zambia. However, little detail of the procedures is presented and it is not possible to evaluate the usefulness of the plant from that report (Muyobela et al., 2015). Although the rotenone-based products that are currently registered in the United States are considered to have a low toxicity, and the World Health Organization has defined it as moderately hazardous class II, the Pesticide Action Network, PAN, based in the United Kingdom makes a case that there is insufficient evidence of safety.

16. CULTIVATION, COLLECTION AND PROCESSING OF HERBAL DRUGS

Pharmaceutical chemicals are mostly derived from medicinal plants, and cultivating these plants provides several benefits for supplying a consistent stream of high-quality raw materials. This study emphasizes the relevance of regulated culture, appropriate seed selection, and efficient propagation strategies for increasing the availability of medicinal plant materials for pharmaceutical and therapeutic applications.

17. CULTIVATION STAGES AND FACTORS INFLUENCING QUALITY

The cultivation of medicinal plants involves several steps, from seed selection to growth and multiplication. Plant growth is greatly influenced by soil characteristics, its ability to store water, and other factors. High-quality seeds with accurate identification and traceability are essential for effective growth. The methods of sexual (seed) and asexual propagation are both used, and each has its own benefits and drawbacks. This work goes in-depth on seed propagation procedures, covering several planting methods and unique treatments to promote germination (Shinde et al. 2009).

18. ADVANTAGES OF CULTIVATION

Growing medical plants have various benefits, including increased output and therapeutic quality of crude pharmaceuticals, higher quality and purity of plant materials, reliable raw material supply, industrialization prospects, and the incorporation of contemporary technical elements. The article also emphasizes how crucial it is to follow the right agricultural practices and keep the soil healthy to accomplish effective agriculture (Srivastava et al., 2020).

19. FACTORS AFFECTING PLANT GROWTH

Plant development is greatly influenced by several variables, including altitude, temperature, rainfall, day length, and soil type. In-depth research on soil fertility, irrigation methods, and the use of fertilizers, manure, and biofertilizers has demonstrated their importance in promoting plant development. This chapter also discusses the difficulties caused by pests, such as bacteria, fungi, viruses, and microorganisms, and provides an overview of effective pest control methods (Zhou et al., 2018).

20. COLLECTION, PROCESSING, AND QUALITY MANAGEMENT

The collection, cultivation, and processing of crude medications are essential for the manufacture of herbal medicines. To achieve optimal potency, timing is essential for drug collection, considering elements such as season and plant age (Shinde et al., 2009). Various plant components were harvested based on their therapeutic potential. Pharmaceuticals were harvested, dried, and dried to remove contaminants after collection. Proper drying procedures, including natural methods such as sun drying and artificial ones like oven drying, maintain quality and stop microbial growth. Garbling is the process of removing foreign objects, whereas packaging and storage require taking temperature, moisture, and insect protection into account.

Testing and documentation are part of quality management, which ensures that the finished product adheres to specified standards (Nafiu et al. 2017).

21. EVALUATION OF CRUDE DRUGS

The evaluation of crude drugs involves various methods for determining their identity, quality, purity, and potency. These methods include organoleptic, microscopic, physical, chemical, and biological methods.

22. EVALUATION OF CRUDE DRUGS

Organoleptic evaluation

This involves using the senses (sight, smell, taste, and touch) to analyze the physical characteristics of the drug. The color, taste, size, shape odor, and texture were observed to identify the drug. For example, form of Talka gum and the color can be distinguished from those of acacia gum.

Microscopic evaluation

Microscopic examination is used to identify small fragments of crude or detect adulterants, powdered herbs, and identify plants based on tissue features. Different stains and reagents reveal characteristic features such as cell walls, starch grains, crystals, trichomes, and fibers. This method helps differentiate similar-looking drugs, such as by identifying different types of rhubarb (Patil et al., 2013).

Physical evaluation

This involves assessing various physical properties of the drug, such as its solubility, specific gravity, refractive index, melting point, moisture content viscosity, optical rotation, and extractive values. These properties can help to identify and characterize drugs. For instance, the refractive index can be used to distinguish between different oils (Kunle et al., 2012).

Chemical evaluation

Qualitative and quantitative chemical tests were used to quantify and identify the specific chemical constituents. Chemical assays determine the content of particular compounds such as alkaloids, volatile oils, glycosides, resins, and vitamins. Instrumental analyses such as chromatography and spectroscopy provide detailed chemical information (Sahoo et al., 2010).

Biological Evaluation

Biological methods assess the pharmacological activity, potency, and toxicity of the drugs. These methods involve testing drugs on living organisms or isolated tissues to observe their effects. Animal models, such as guinea pigs, rabbits, mice, and pigeons, are used to study various activities, such as oxytocic, mydriatic, and cardiac effects. Microbiological assays were used to evaluate the antimicrobial properties (Kamboj et al., 2012). Toxicity studies have assessed lethal and effective doses of the drug in animal models. Symptomatic and tissue/organ methods were used to evaluate the various effects. For example, mice are used in toxicity studies, and isolated organs like rabbit's eyes or intestine are used for specific assessments. In summary, the evaluation of crude drugs encompasses a range of methods that utilize sensory perception, microscopy, physical measurements, chemical analyses, and biological assays to comprehensively characterize their properties and effects (Khan et al., 2022).

23. ROLE OF MEDICINAL PLANTS ON NATIONAL ECONOMY

The use of medicinal plants for various purposes, including healthcare, food and fragrance, has been a significant part of human history across cultures. Traditional medicines have played a vital role in Asia and other parts of the world, particularly those rooted in the use of plants, serving both preventive and curative needs. Medicinal plants remain a crucial national resource, supporting livelihoods and providing healthcare solutions. Traditional medicine, frequently based on plants, is a major source of healthcare for a sizeable section of the population in many developing nations, including Asia. About 80% of the populace in poor nations still uses traditional medicines today, with plant-based medications making up a substantial percentage of pharmaceuticals (Pandey and Shukla, 2008). The value of therapeutic plants is significant economically. Rural and tribal communities that gather materials from forests or grow them on farms profit from the sale of these plants. The genetic diversity of these resources is, however, at danger due to unsustainable practices such destructive harvesting. The market for herbal and plant-based products, including nutraceuticals and cosmeceuticals, is experiencing growth worldwide. Medicinal plants hold promise in the development of new drugs and products, contributing to economic growth. The industry's expansion is particularly evident in the food supplement and personal care sectors. Plant-based medicines and products have a bright future. Their significance in national economies is highlighted by the rising demand for these items, their economic value, and their potential to enhance healthcare. An effective herbal medicine sector can be developed by cooperative efforts between farmers, research facilities, governments, and businesses, which is advantageous for both the economy and public health. In conclusion, medicinal plants have been important throughout history in many facets of human life. With the potential for additional expansion and contribution to national economies, they remain a crucial resource for healthcare, economic development, and cultural practices (Zahra et al., 2020).

24. DRUGS CONTAINING ALKALOIDS

A wide variety of nitrogenous chemical molecules known as alkaloids can be found in fungi, animals, and plants. Since they frequently originate from amino acids, they can have a variety of pharmacological effects. Alkaloids from over 10,000 distinct plant families have been identified. They often feature complicated ring structures, nitrogen content, and get their names from their alkaline qualities. Alkaloids have important medical uses, such as pain relief, antimalarial, and anti-inflammatory effects, and they may immobilise huge animals in little doses. True alkaloids, which are produced from amino acids, protoalkaloids, which have a N atom outside of a heterocyclic ring, and pseudoalkaloids, which come from non-amino acid antecedents, are the three types of alkaloids. They are further categorised as phenylethylamine, tropane, indole, quinoline, and terpenoid alkaloids based on their chemical compositions and places of origin (Schmeller and Wink, 1998). The happening of alkaloids is widespread in nature, primarily in higher plants but also in lower plants, animals, and even bacteria. Alkaloids share characteristics including being colourless, crystalline solids, possessing ring structures, and frequently tasting bitter. There are several ways to extract them, including treating with alkaline materials and then extracting with organic solvents. To find and confirm the presence of alkaloids in a sample, scientists utilise chemical tests such the Dragendorff's, Mayer's, Hager's, Wagner's, and tannic acid tests. The numerous impacts and possible uses of these substances, which have been employed by civilizations for thousands of years, continue to be of significant interest. The Solanaceae family of plants, including belladonna (*Atropa belladonna*), datura (*Datura spp*.), and hyoscyamus (*Hyoscyamus niger*), frequently contain the tropane alkaloids hyoscyamine, atropine, and hyoscine (scopolamine). Although these alkaloids are used medicinally in many different ways, they are also infamous for being toxic. The pyrrolidine and piperidine rings make up the tropane ring structure. Atropa belladonna is the source of belladonna, sometimes referred to as deadly nightshade, which contains alkaloids including hyoscyamine and atropine. For peptic ulcers, digestive issues, and to manage excessive gastrointestinal and urinary tract motor activity, it is utilised as an adjuvant therapy. Hyoscine and hyoscyamine are found in Datura, particularly *Datura stramonium* and *Datura metel*. It is used to treat pain, promote sleep, and treat asthma. To alleviate respiratory problems, datura leaves can be smoked. Hyoscyamine and lower levels of atropine and hyoscine are present in *Hyoscyamus niger*, also known as henbane. It is used to treat asthmatic bronchial spasms and is an antispasmodic, anodyne, and sedative (Roeder and Wiedenfeld, 2013).

These plants have a long history of usage in traditional medicine, but if not administered properly, their powerful alkaloid content could make them hazardous. The tropane alkaloids affect the neurological system and have sedative and anticholinergic effects. They have historically been used for a variety of things, such as promoting sleep, relieving pain, and controlling some medical disorders. However, care should be taken when using or handling these plants or any of their derivatives due to their toxicity. Ergot is a fungal parasite that infects the ovaries of rye plants, resulting in the formation of a hard, dark-purple sclerotium called ergot. This ergot contains a variety of alkaloids, including ergonovine (ergometrine) and ergotamine, which have different physiological effects. Ergonovine is an oxytocic compound used to assist in childbirth and reduce post-partum bleeding, as it stimulates uterine muscles. Ergotamine and its derivatives are employed as analgesics for treating migraines. The ergot alkaloids can be categorized into clavine-type alkaloids and lysergic acid derivatives. Lysergic acid diethylamide (LSD-25) is a well-known psychotomimetic compound derived from lysergic acid, which is linked to various psychological effects (Agarwal et al., 2023).

The asexual sphacelia stage, the sexual sclerotium stage, and the ascospore stage are the three stages of the ergot life cycle. Ergot sclerotia are produced when the fungus infects rye plants through spores spread by wind or insects. Ergometrine and ergotamine are the two main alkaloids present in this complex mixture of sclerotia. Ergot's medical uses range from assisting childbirth and preventing post-partum hemorrhage with ergonovine to treating migraines with ergotamine derivatives. Additionally, the psychedelic effects of lysergic acid diethylamide (LSD-25) have been of interest in psychological research. Vinca, also known as *Catharanthus roseus* or *Madagascar periwinkle*, is a plant belonging to the Apocynaceae family. It is native to Madagascar but is found in various tropical and subtropical regions around the world. Vinca is cultivated for its medicinal properties and is used in both traditional and modern medicine. Perennial in nature, the plant prefers different kinds of soil and lighting. It is grown by spreading the seeds in nurseries, and the seedlings are then moved into the fields. For medical purposes, the entire plant is harvested, including the leaves, stems, blossoms, and roots. The flowers might be violet, pinkish white, or carmine red, and the leaves are green and elliptical or oblong in shape. Vinca's dorsiventral leaves have distinctive epidermal layers, trichomes, stomata, and vascular bundles, as seen under a microscope. With over 90 alkaloids found, including ajmalicine, serpentine, and tetrahydroalstonine, alkaloids are the main chemical components of vinca. The dimeric indole alkaloids vinblastine and vincristine, which have strong anticancer effects, are the most important alkaloids. Other indole alkaloids found in vinca include vindoline and catharanthine, as well as monoterpenes, sesquiterpenes, and glycosides. While vincristine is used as a cytotoxic drug to treat paediatric leukaemia, vinblastine is used as an antitumor agent to treat Hodgkin's disease. In herbal therapy, vinca is also used for its astringent and tonic characteristics to treat diabetes, menorrhagia, bleeding piles, scurvy, and sore throats (Mahalakshmi et al., 2019). Vinca alkaloids have been included into medication compositions. For instance, Cipla sells a medication called Cytocristin that contains vinca alkaloids. Overall, Vinca is a useful plant in the medical profession due to its medicinal properties, especially its strong anticancer alkaloids. *Physostigma*, commonly known as Calabar bean, is a plant whose dried ripe seeds, containing at least 0.15% alkaloids, are used for medicinal purposes. It belongs to the Leguminosae (Papilionaceae) family. Indigenous to West Africa, Old Calabar, India, and Brazil, the plant has a notable history of being used as an ordeal due to its extreme toxicity. The plant is characterized by twining climbers, purplish bean-like flowers, and kidney-shaped seeds found in dark brown pods. The major alkaloid present in *Physostigma* is physostigmine, also known as eserine, which is recognized for its medical applications. Other alkaloids include eseramine, geneserine, and physovenine. *Lobelia*, also referred to as Indian tobacco or Pukeweed, is sourced from the dried aerial parts of *Lobelia inflata*, a plant in the Lobeliaceae family. Indigenous to Eastern and Central United States, Canada, and India, *Lobelia* is a biennial herb with erect stems, pinnately toothed leaves, and pale violet-blue flowers. It is cultivated and collected for its medicinal properties, which are attributed to alkaloids present in the plant, particularly lobeline. Lobeline is the main active alkaloid, and other related alkaloids include lobelidine, lobelanidine, lobelanine, and isolobinine. Lobelia also contains gum, resin, chlorophyll, fixed oil, lignin, salts, and other compounds. Both *Physostigma* and *Lobelia* have been utilized for their medicinal effects. *Physostigma*'s physostigmine is used for its impact on the eyes, causing pupil contraction and affecting vision, as well as its stimulation of unstriped intestinal muscles in cases of chronic constipation. *Lobelia*, on the other hand, contains lobeline, which has various effects on the body, including respiratory and nervous system effects. In summary, *Physostigma* and *Lobelia* are two plant sources of alkaloids that have been traditionally and pharmacologically used for their respective medicinal properties (Gutiérrez-Grijalva et al., 2020).

Quinoline alkaloids are a class of compounds characterized by a double carbon ring containing one nitrogen atom. One well-known example is quinine, derived from the bark of *Cinchona ledgeriana*, a tree native to South America. Quinine is notable for its effectiveness in treating malaria, as it is toxic to various species of Plasmodium protozoans, which cause the disease. These organisms invade red blood cells, multiply within them, and lead to the characteristic fever and chills associated with malaria. Quinine's discovery dates back to the 17th century when Spanish Jesuits in Peru used bark extracts from the quina tree (*Cinchona officinalis*) to cure malaria, leading to its use in medical practice. Despite the development of synthetic analogs, natural quinine remains valuable due to its efficacy against certain drug-resistant strains of Plasmodium. Cinchona, also known as Cortex Cinchonae, Peruvian or Jesuit's bark, is the dried bark obtained from various species of the Cinchona plant, belonging to the Rubiaceae family. It is primarily sourced from tropical valleys in the Andes, particularly in Bolivia and Southern Peru. The historical use of cinchona dates back to 1638 when it was discovered as an effective antimalarial remedy. The Spanish missionaries played a crucial role in promoting the use of cinchona bark for approximately two centuries. Cultivation of cinchona involves seed sowing, careful nurturing of seedlings, and transplanting them to suitable soil and climate conditions. The bark is collected from mature trees, typically between 6 to 9 years of age, during the rainy season. It is characterized by its distinctive bitter and astringent taste, curved or quill-like shape, and varies in color based on the species. Microscopic examination of the bark reveals cork, cortex, phloem, and other cell types. The bark contains over 30 alkaloids, with quinine, quinidine, cinchonine, and cinchonidine being the chief constituents. These alkaloids have antimalarial properties and are stereoisomers of each other. Other components present in cinchona include bitter glycosides, starch grains, calcium oxalate crystals, and quinic acid (Wijnsma and Verpoorte, 1988).

Cinchona bark is known for its various medicinal uses. It is primarily used as an antimalarial agent, and its alkaloids exhibit analgesic, antipyretic, and tonic properties. Quinidine, one of the alkaloids, has cardiac depressant effects, while cinchonidine is utilized for rheumatism and neuralgia. Despite its efficacy, cinchona bark is sometimes substituted with other plant species like Cuprea Bark (*Remijia pedupiculato*) that contain similar alkaloids. Cinchona bark is an important ingredient in several pharmaceutical preparations, such as Herbipyrin tablets and M.P. 6 Capsules by Vasu Healthcare. The historical significance, cultivation methods, and alkaloid-rich composition make cinchona a valuable and versatile natural resource in the field of medicine. Ashwagandha, also known as Withania root or Clustered Wintercherry, is derived from the dried roots and stem bases of the plant *Withania somnifera*, which belongs to the Solanaceae family. This herb has a rich history in Ayurvedic medicine, with usage dating back over 3,000–4,000 years. It has been described in sacred texts like Charaka and Sushruta Samhitas as a tonic for various purposes, including emaciation, enhancing reproductive function, and promoting vitality (Swain et al., 2022). The cultivation of Ashwagandha involves propagation through seeds, cuttings, or division. It thrives in well-drained, slightly alkaline soil with full sun to partial shade. The plant is recognized by its low-lying stature, often reaching 1–2 ft (occasionally up to 6 ft) and its characteristic bitter and mucilaginous taste. The roots are straight, unbranched, and conical, with varying thickness based on age. Microscopic examination of Ashwagandha root reveals cork, secondary cortex, phloem, and other cellular components. It contains various alkaloids, with withanine being the primary constituent. Other alkaloids present include somniferine, pseudowithanine, tropine, pseudotropine, hygrine, isopellederine, anaferine, and anahygrine, along with steroid lactones. The leaves of Ashwagandha contain steroid lactones called withanolides. Ashwagandha is used in traditional medicine for its adaptogenic properties, making it valuable for treating nervous disorders, intestinal infections, and leprosy. It acts on the nervous and reproductive systems, rejuvenating the body and aiding recovery after chronic illness. It is also employed to address conditions such as nervous exhaustion, insomnia, impotence, infertility, multiple sclerosis, and more. Externally, it is applied as a poultice for boils and painful areas. In the market, Ashwagandha is featured in various formulations, including tablets, syrups, and oils. It is a component of products like Abana, Geriforte, Tentex forte, and more, offered by companies such as Himalaya Drug Company and Baidyanath.

25. ISOLATION OF PHYTOPHARMACEUTICALS

The text discusses a variety of alkaloids found in fungi, animals, and plants, highlighting their pharmacological effects and medical uses. Alkaloids are categorized into true alkaloids, protoalkaloids, and pseudoalkaloids, with different chemical compositions. The Solanaceae family of plants contains tropane alkaloids like hyoscyamine and atropine, used for medicinal purposes but known for their toxicity. Ergot, a fungal parasite, produces alkaloids like ergonovine and ergotamine, with medical uses ranging from aiding childbirth to treating migraines. Vinca plants yield alkaloids like vinblastine and vincristine, effective against cancer. Physostigma and Lobelia offer medicinal alkaloids, and quinoline alkaloids like quinine combat malaria. Cinchona bark, the source of quinine, has rich historical and medicinal significance.

Ashwagandha contains alkaloids beneficial for various health conditions. Additionally, the text mentions the alkaloids caffeine, aconitine, and ephedrine, with their biological sources, characteristics, uses, and potential toxicity. Care should be taken when considering these alkaloids for medical purposes, and information should be cross-referenced from reliable sources (Al-Harrasi et al., 2022).

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CHAPTER 5

NATURAL BIOACTIVE COMPOUNDS OF MEDICINAL PLANTS: USE IN ANTICANCER TREATMENT

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INTRODUCTION

Cancer is a neoplastic and genetic illness that is the result of the body's uncontrolled proliferation of abnormal cells and their metastasis to other areas of the body. There is an unbalance between division of cells and cell death in cancer (Nagai and Kim, 2017). Furthermore, cancer begins with DNA mutations, and the irreversible alterations in the DNA provide the basis for the cell to become cancerous (Ansil et al., 2014). The 2nd leading reason for mortality worldwide is cancer, behind cardiovascular disease, and it is also a global challenge, increasing annually (Mathers and Loncar, 2006). Up till now, over 277 cancer kinds have been recognized and determine with prostate, breast, lung, colon, rectum, bronchus, and urinary bladder cancers being the most common (Wogan et al., 2004). The World Health Organization (WHO) predicts that the number of cancer deaths will increase from 7.1 million in 2003 to more than 13.1 million by 2030 (Mousavi et al., 2009; Mathers and Loncar, 2006). Therapeutic strategies perform a crucial part in efficiently curing cancer (Cameron et al., 2019). Chemotherapy, radiotherapy, immunotherapy, hormone therapy, chemically derived medicines, and surgery are the most frequent therapeutic modalities used to treat cancer. Chemotherapeutics, which is based on a number of chemical compounds, has been for years the main cancer cure approach, but, in most cases, undesirable side effects are associated with it and adversely affect healthy cells (gastrointestinal disorders, kidney damage, hair follicle damage, and other complications). Also, these factors, combined with over time the problem of drug resistance and the high cost of conventional cancer therapies considerably vitiate a cancer patient’s quality of life (Aiello et al., 2019). Although cancer has been a continual fight across the world and important advances in the cure and management of cancer progression have been accomplished, considerable inadequacies and potential for development keep. Chemoprevention is a cutting-edge method of cancer management. Some cancer cells have developed strategies to avoid death from particular pharmacological therapies by modifying a few endogenous protein isoforms, enhancing cellular expression of specific efflux proteins, and suppressing apoptotic activity paths. In the research of several cancer cells' sensitivity to plant compounds as alternative therapy options, these pathways have been discovered along with others. Medicinal plants and their related phytocompounds as a combination cure with chemotherapy can be one of the viable methods intended to inhibit, prevent, or reverse malignancy before the occurrence of invasive cancer and also lessen side effects (Yin et al., 2013). In this respect, there is tremendous research and trade engaged in generating novel anticancer medicines using organic resources, and studies devoted to producing those have become a prominent research topic (Kinghorn et al., 2003). The chapter's goal is to draw attention to the natural bioactive substances derived from medicinal plants that have the ability to fight cancer and function as antioxidants.

1. BIOACTIVE COMPOUNDS OF MEDICINAL PLANTS

Nature is an appealing source of potential curative operatives acquired from the extensive diversity of substances that exist in a billion species of plants. The countless varieties of plants provide excellent potential to create new anticancer medications (Gullett et al., 2010). Plants have long been a basis for the traditional medicine systems for their natural antiseptic properties and they have provided continuous remedies to the mankind for thousands of years due to its easy availability, lower cost, non-toxic, safe and less frequent side effects (Nussbaumer et al., 2011; Shah et al., 2013). The isolation and development of herb-originated chemicals with pharmacological characteristics, notably in the development of cancer chemotherapy drugs, may enhance the effectiveness of common chemotherapy medicines (S Liberio et al., 2013). According to Newman and Cragg (Newman and Cragg, 2016), around 35% of all anticancer medicines accessible for the cure of cancer across 1981 and 2014 were obtained from plant compounds. Plant extracts are acknowledged as having strong bio-resources, medicinal values, and cure agents for various types of cancer. Medicinal plants and their derivative phytocompounds, which relate to the drug products of herb stems, roots, leaves, bark, and seed, contain several bioactive molecules and phytochemical components and numerous structurally and functionally various metabolites that have crucial roles in cancer treatment (Wang et al., 2019). These phytochemicals have shown considerable antioxidant properties by scavenging free radicals, quenching ROS, and blocking oxidative enzymes, and some phytochemicals are known to have direct, particular anticancer activities. Bioactive chemicals cause cytotoxicity in tumor cells by activating the intrinsic and/or extrinsic apoptotic pathways, blocking telomerase, and restricting cell proliferation by stimulating a variety of signaling cascades. They can also be utilized as alternative compounds in chemotherapy and cancer target therapies (Ganesan and Xu, 2017). The studies showed the antitumor activity and cancer cell inhibition activity of medicinal plant acquired chemicals may be provided to several types of mechanisms, such as:

A: Secondary metabolites in plant extracts have impacts on cytoskeletal proteins that function a significant role in cell division, DNA damage and activation of apoptosis-inducing enzymes, inhibition of DNA topoisomerase enzymes, antiprotease, or antioxidant activities (Kola et al., 2022).

B: Plants and their major combinations influence transcription and the cell cycle through several processes, including:

- Stimulation of superoxide dismutase to remove free radicals,
- Decrease in DNA oxidation,
- Induction of apoptosis via cell cycle arrest in the S phase,
- Decrease of PI3K, P-Akt protein, and MMP expression,
- Decrease of antiapoptotic Bcl-2, Bcl-xL proteins,
- Reduction of proliferating cell nuclear antigen (PCNA), cyclin A, cyclin D1, cyclin B1, and cyclin E. (Dixit and Ali, 2010).

Plant chemicals also raise the amounts of cell cycle inhibitors such p53, p21, and p27, as well as BAD, Bax, caspase 3, caspase 7, caspase 8, and caspase 9 proteins (Aiello et al., 2019). Recently, novel treatment mechanisms in cancer cells have been addressed. In this perspective, novel organic anticancer agents provide potential prospects in cancer patient care (Rad et al., 2018). About 35,000 varieties of plants have been examined by the National Cancer Institute (NCI) for anticancer properties. Almost 3,000 of these plant species have proven repeatable anticancer action (Desai et al., 2008). Plants generate a plethora of functionally and structurally varied metabolites that perform a variety of functions in plant growth and evolution and also in plant reactions to changing surroundings and abiotic and biotic stressors (Wang et al., 2019). Secondary metabolites, as phytochemicals, are accountable for the medicinal estates of the plants to which they belong. Secondary metabolites extracted from plants that have a variety of pharmaceutical characteristics and biologic effects, like anticancer, antioxidant, and anti-inflammatory activity, are subdivided into three major classes: Secondary metabolitesics compounds (phenolic compounds) (Flavonoids and phenolics) (~8,000 types), terpenoid (~25,000 types), and alkaloids (~12,000 types) (Cosme et al., 2020; Linnewiel-Hermoni et al., 2015).

2. ANTICANCER ACTIVITIES OF PHENOLIC COMPOUNDS

2.1. Anticancer Effect of Polyphenols

Polyphenols are bioactive molecules of plant secondary metabolites synthesized by plants, universal in the plant kingdom, and seldom exist in bacteria, fungi, and algae. Polyphenols are extensively found in a variety of higher plant parts, such as; vegetables, fruit, spices, grains, legumes, and nuts. (Quideau et al., 2011). Phenolic substances have an analogous chemical structure that consists of an aromatic ring with one or more hydroxyl substituents. They may range from basic molecules like phenolic acids to highly polymerized compounds like tannins, and they are categorized into several kinds depending on their basic chemical structure (Lugasi, 2003). The major subgroups of phenolic compounds involve phenolic acids, flavonoids, stilbenes, and lignans (Bhosale et al., 2020). The production of phenolic compounds involves two major processes: the shikimic acid system and the malonic acid pathway, with the former being the primary mechanism in herbs (Lattanzio, 2013).

The inherent antioxidant, antibacterial, anticarcinogenic, and anti-inflammatory features of phenolic combinations have recently been a hot spot in terms of investigation and application. Free radical-scavenging characteristics of polyphenols help prevent such oxidative stress-related chronic diseases as cancer, cardiovascular disease, and neurological disease (Li et al., 2014). Polyphenols have anticancer properties via a variety of methods, including cancer cell elimination via signaling pathway alteration, influencing cell proliferation stages via arresting the G2/M cell cycle and inhibiting topoisomerase II, cell cycle suppression, antiangiogenic, antimetastatic, and apoptosis induction (Abbas et al., 2017). Polyphenols are hypothesized to initiate apoptosis by modulating the mobility of copper ions that are bound to chromatin, causing DNA fragmentation. Moreover, phenolic chemicals have anticancer properties via the pathways of phosphoinositide 3-

kinase (PI3-K) and protein kinase B (Akt). Research has shown that inhibiting PI3-K activity restrains phosphorylation of Akt and the mammals target of rapamycin (mTOR), resulting in decreased activity of nuclear factor kB (NF-kB). By this method, the transcription and synthesis of proteins that control the cell cycle are restrained, accordingly reducing the growth of cancer cells and increasing cell death (Ramos, 2008; Memmott and Dennis, 2009).

The Common Polyphenols in Herbals with Antitumor Activities

The chemical structure and herbal source of common polyphenols with antitumor potential containing curcumin, gingerol, oleuropein, eugenol, gossypol, protocatechualdehyd, and rosmarinic acid are shown in (Figure 1).

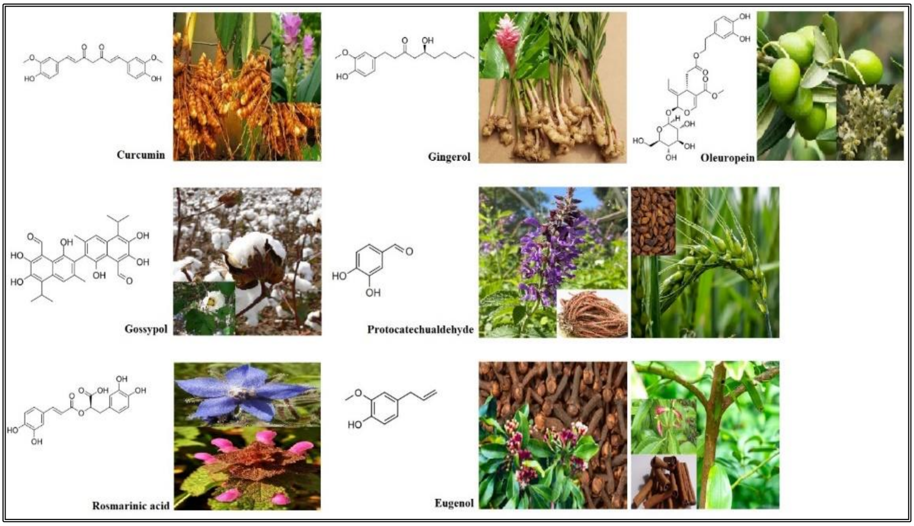

Figure 1: The chemical structure and herbal source of common polyphenols with antitumor potential.

Curcumin

Curcumin (Figure1) comprises polyphenolic compounds obtained from the Curcuma longa (turmeric) rhizome. Turmeric, scientifically known as Curcuma longa, is a flowering plant in the Zingiberaceae family with an underground stem known as a rhizome (Ammon and Wahl, 1991). Curcumin (diferuloylmethane) is a miraculous chemical with antioxidant and anticancer capabilities as the active element of Zingiberaceae (Girardi et al., 2018). The anticancer properties of curcumin over devers cancers, such as leukemia, lymphoma, digestive, breast, ovary, lung, colon cancers, and brain tumors, have been demonstrated (Anand et al., 2008). Actually, curcumin's combined antioxidant, anti-inflammatory, antiproliferative, anti-angiogenic, anti-metastatic, cell cycle restraints, and proapoptotic effects result in an inhibitory impact on cancer via modulating genes, restraints of tumor creation, and molecules engaged in these pathways. The antiproliferative property of curcumin can lead to associated with its capability to down-regulate the expression of a few genes, such as NF-kappa B, activator protein 1 (AP-1), epidermal growth receptor 1 (EGR-1), cycloxygenase 2 (COX2), lysyl oxidase (LOX), nitric oxide synthase (NOS), matrix metallopeptidase 9 (MMP-9), and tumor necrosis factor (TNF) (Shao et al., 2002; Surh et al., 2001). Turmeric also decreases the expression of certain chemokines, cell surface adhesion molecules, cyclins, and growth factor receptors, such as the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (HER2) (Aggarwal et al., 2003). A few research have demonstrated that curcumin exerts antiproliferative and apoptotic effects via inhibiting protein tyrosine kinase activity, inhibiting protein kinase C activity, suppressing c-myc mRNA levels, and up-regulating B-cell lymphoma 2 (Bcl-2) mRNA expression (Chen and Huang, 1998). Curcumin induces apoptosis by causing a fast drop in mitochondrial membrane potential, the release of cytochrome c, the activation of caspases 3 and 9, and the downregulation of the anti-apoptotic proteins Bcl-XL and Inhibitor of Apoptosis Protein (IAP) (Rashmi et al., 2004; Jana et al., 2004). Curcumin and its compounds revealed substantial inhibition of VEGF and bFGF-mediated corneal neovascularization and immediately restrained angiogenesis in vivo and in vitro (Kerbel and Folkman, 2002). Goel et al constituted that curcumin effectively restrained the expression of COX-2 in human colon cancer cells and in COX-2 none- pressing cell lines without modifying the expression of COX-1. This is a significant advantage of curcumins because extended utilize of nonsteroidal anti-inflammatory drugs (NSAIDs) and non-specific inhibition of COX-1 causes unwanted gastrointestinal and renal adverse effects (Sharma et al., 2011)

Gingerol

Gingerol ([6]-gingerol) (Figure1) is a phenolic phytochemical compound that exists in fresh ginger. Zingiber officinale Roscoe, commonly referred to as ginger, is a herbaceous flowering plant in the Zingiberaceae family (Banerjee et al., 2011). The bioactive constituents of ginger rhizome such as volatile oils, anthocyanins, tannins, phenolic compounds, and sesquiterpenes. Ginger's anticancer qualities have been associated with phenolic compounds, which include gingerols, shogaols, and paradols (Mao et al., 2019). The anticancer potential of ginger against cancers, including cervial, breast, liver, colorectal, endoretrial, prostate, melanoma skin, and colon cancers, has been shown (Prasad and Tyagi, 2015). Regarding the anticancer activity, ginger and its constituents inhibit the proliferation, cell division, trigger of apoptosis, and differentiation of several kinds of cancer cells in vitro (Li et al., 2012). Some studies have demonstrated that 6-gingerol can hinder NF-KB activation and boost the expression of the caspase 3 and 9 genes in liver cancer (Zadorozhna and Mangieri, 2021). Ginger extracts effectively reduce ovarian cancer cell growth by raising P53 expression and triggering apoptosis (Pashaei-Asl et al., 2017). Ginger also restrained skin cancer cell growth and proliferation by inducing apoptosis via changes in the BAX/Bcl-2 proportion (Nigam et al., 2009). Ginger leaves may induce apoptosis and decrease cell viability, in human colorectal cancer cells leading to enhanced ATF3 expression through activation of the ATF3 promoter (Park et al., 2014).

Oleuropein

Oleuropein (Olea europaea) (Figure1) is a phenolic substance obtained from olives that is strong in antioxidants and has anti-cancer effects. Olea europaea L., generally referred to as olive, relates to the Oleaceae family (Bayat et al., 2019). Because of the existence of specific phenols, including oleuropein, hydroxytyrosol, oleanolic acid, cholinergic acid, and maslinic acid, olives have been demonstrated to have antioxidant, anti-inflammatory, chemopreventive, and anti-proliferative potential (Borzì et al., 2018). According to research, phenolic compounds found in olive produce have anticancer activity via decreasing cell growth and survival, inhibiting cell proliferation, migration, and invasion, modulating cell cycle phases, and inducing apoptosis in various tumor models, so they can help reduce cancer risk by delaying the development, progression, or the return of different kinds of tumors (Emma et al., 2021). Acids, lignans, phenols, flavonoids, and secoiridoids are the bioactive components derived from olive leaves (Nediani et al., 2019). Oleuropein, the basic phenolic compound of olive leaf extract, has been found to be cytotoxic to human breast cancer (Fu et al., 2010) and hepatocarcinoma cells (Katsoulieris, 2016). In addition to other anticancer effects, pinoresinol, another component of olive oil, has an effect on colon cancer (Fini et al., 2008).

Eugenol

Eugenol (4-allyl-2-methoxyphenol) (Figure1) is a natural phenolic combination obtained from Syzigium aromaticum (cloves) and cinnamon (Barboza et al., 2018). Aromatic herbs like nutmeg, basil, and bay leaves also comprise eugenol. The molecular mechanism of eugenol-induced apoptosis has been confirmed in melanoma, skin cancer, osteosarcoma, leukemia, gastric, and mast cells. (Jaganathan and Supriyanto, 2012). Eugenol can limit tumor development, spread, and occurrence following treatment. Eugenol reduces IL-8 and IL-6 production by inhibiting NF-B signaling, making it a therapeutic candidate through BCSC suppression (Islam et al., 2018).

Gossypol

Gossypol (Figure1) is a polyphenol extracted from the cotton plant's seed, roots, and stem. Cotton grains contain a tiny amount of the polyphenol chemical gossypol. Scientists investigated gossypol's anticancer impacts on a different of cancer cell lines, including prostate, breast, ovarian, leukemia, pancreatic, and melanoma (Clément, 2017). Gossypol has been demonstrated to suppress important nuclear enzymes involved in DNA replication and repair, such as DNA polymerase and topoisomerase II, also inhibit DNA synthesis in HeLa cells (Balakrishnan et al., 2008). In the MM468 and MM231 breast cancer cell lines, gossypol significantly boosted the expression of BCL2 interacting protein 3, tumor necrosis factor receptor superfamily 9, growth arrest, and DNA damage-inducible 45 alpha protein (Messeha et al., 2019).

Protocatechualdehyde

Protocatechualdehyde (Figure1) is a polyphenol compound obtained from the herb Salvia miltiorrhiza root and the leaves of barley tea plants (Jeong and Lee, 2013). Procatechualdehyde exhibits proapoptotic and anti-proliferation characteristics in human colorectal cancer cells. Procatechualdehyde inhibits β-catenin expression via NF-B and glycogen synthase kinase-3 beta (GSK-3)-mediated degradation by proteasomal enzymes. Protocatechualdehyde also restrained cyclin D1 expression by proteasomal degradation, independent of β-catenin (Choi et al., 2014).

Rosmarinic acid

Rosmarinic acid (Figure1) is a phenolic compound that is frequently obtained in the Boraginaceae and Lamiaceae families of plants(Noor et al., 2022) . Rosmarinic acid demonstrates anticancer properties via controlling oxidative stress, chronic inflammation, cell cycle arrest, apoptosis, and metastasis (Han et al., 2018). Rosmarinic acid has the ability to restrain the expression of miR-155-5p in three colon cancer cell lines: HCT-8, HCT-116, and Ls174-T. Rosmarinic acid can suppress the STAT3 pathway by reducing miR-155-5p levels, hence inhibiting the cancer cell glycolysis process and proliferation of tumor cells (Zhang et al., 2021).

2.2. Anticancer Effect of Phenolic acids

Phenolic acids, which are composed of a single phenolic ring with several hydroxy or methoxy groups connected to their backbone, are a prominent and simplest family of phenolic compounds that have anticancer effects with diverse mechanisms (Cháirez-Ramírez et al., 2021). Phenolic acids are classified into two subgroups: hydroxybenzoic acid (HBA) and hydroxycinnamic acid (HCA). Phenolic acids and derivatives of them have illustrated inhibition of the angiotensin-converting enzyme, with consequent chemopreventive and chemotherapeutic activities.

HBAs have a C6-C1 structure and involve p-HBA, protocatechuic, vanillic, salicylic, gallic, ellagic, and syringic acids. HBAs are plentiful in oilseeds, cereals, coffee, tea, cinnamon, kiwis, cowpea, black currant, raspberry, squash shells and seeds, apples, plums, cherries, blueberries, and blackberries. (Zhang et al., 2022a). HCAs, which include coumaric, caffeic, ferulic, and sinapic acids, are aromatic molecules containing an unsaturated 3-carbon side chain (C6-C3). Coffee, cherries, cereals, peaches, spinach, citrus juices and fruits, plums, tomatoes, potatoes, and almonds are the main sources of HCAs (Abramovič, 2015).

2.2.1. The common phenolic acids in herbals with antitumor activities

The chemical structure and herbal source of common phenolic acids with antitumor potential containing chlorogenic acid, gallic acid, and vanillic acid are shown in (Figure 2).

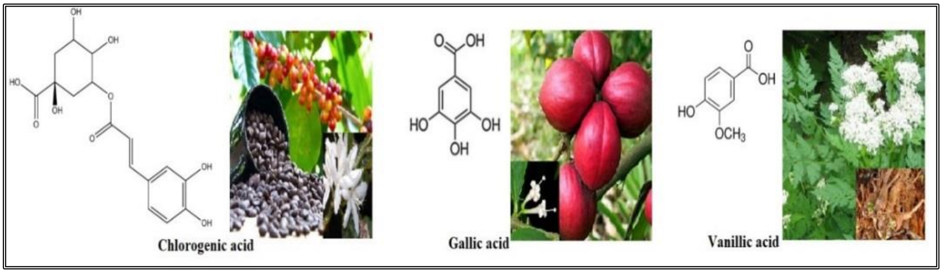

Figure 2: The chemical structure and herbal source of common phenolic acids with antitumor potential.

Chlorogenic acid

Chlorogenic acid (CGA) (Figure 2), also deemed coffee tannic acid and 3-caffeoylquinic acid, is a kind of phenolic acid (phenyl acrylate polyphenol component) found in coffee (Meng et al., 2013) . Chlorogenic acid is created by plants via the shikimic acid pathway during aerobic respiration (Fu et al., 2017). CGA is broadly abundant in higher dicotyledonous plants, ferns, and many Chinese medicine herbs, which have earned the renown of plant gold (Wang et al., 2022). CGA's biological functions are mostly described as antioxidant, antibacterial, anti-tumor, and anti-inflammatory. Research has accumulated to show that CGA reduces migration and invasion while triggering apoptosis in several cancer cell types, involving as colon, breast, and lung (Zeng et al., 2021a). Chlorogenic acid was proven to have anticancer properties by causing distinction in cancer cell lines by increasing KHSRP, p53, and p21, decreasing poor distinction-related genes c-Myc and CD44, and downregulating oncogenic miRNA-17 family members (Huang et al., 2019).

Gallic acid

Gallic acid (Figure 2), the active ingredient, is a poly hydroxy phenolic molecule and a natural antioxidant found in a number of organic products such as grapes, strawberries, bananas, green tea, and vegetables (Sun et al., 2002). In research, gallic acid was derived from the fruit extract of Phaleria macrocarpa and was reported to be involved in the activation of apoptosis in prostate, breast, lung, leukemia, and colon cancer (Sohi et al., 2003). It also acts to inhibit malignancy transition and cancer development by triggering apoptosis and cell cycle arrest (Khalid et al., 2016). Gallic acid has effective antioxidant action, which is evidenced by the rise in damage to DNA and the release of cytochrome c (Subramanian et al., 2015). Gallic acid reduced mitochondrial membrane potential in a time-dependent way and caused cytosolic cytochrome c release, increasing caspase-9 and caspase-3 activation and eventually causing apoptotic cell death (Lo et al., 2010).

Vanillic acid

The root of Angelica sinensis, a Chinese herb utilized in traditional medicine, contains the largest quantity of vanillic acid (Figure 2) known in plants (Circosta et al., 2006). Vanillic acid is a potent preventor of hypoxia-inducible factor 1 (HIF-1) and can significantly decrease the development of tumors in a xenografted tumor model, providing a new viewpoint for understanding how it works to fight cancer (Gong et al., 2019).

2.3. Anticancer Effect of Flavonoids

Flavonoids, once known as vitamin P, are a wide family (with above 6,000 members) of varied polyphenolic compounds obtained in brightly colored fruits, vegetables, cereals, legumes, barks, roots, stems, flowers, tea, chocolate, and wine (Panche et al., 2016). Chemically, flavonoids have a 15-carbon structure that is made up of two phenyl rings and a heterocyclic ring. C6-C3-C6 is the abbreviation for this carbon structure (Dias et al., 2021). Flavonoids have significant medicinal potential owing to their diverse biological features, which contain anti-cancer, antiviral, antibacterial, anti-inflammatory, and antioxidant effects (Ullah et al., 2020). Actually, flavonoids have anticancer properties via several pathways. Flavonoids have the ability to trigger apoptosis in cancer cells via intrinsic and/or extrinsic routes (Millimouno et al., 2014). Flavonoids have also demonstrated significant antiangiogenic effects by regulating the expression of many factors, including VEGF, matrix metalloproteinases (MMPs), and the epidermal growth factor receptor (EGFR). Other processes implicated in flavonoids anticancer actions owing to the control of numerous signaling cascades involve the suppression of the NFkB, PI3-K/AkT, and ERK1/2 signaling pathways of topoisomerase and protein kinases (Raffa et al., 2017; Madunić et al., 2018).

Isoliquiritigenin

Isoliquiritigenin (ISL) is a flavonoid of the chalcone class that is acquired from licorice compounds. Based on scientific research, isoliquiritigenin possesses anti-cancer activity via decreased proliferation, cell cycle disruption, angiogenesis down-regulation, metastasis suppression, and apoptosis induction (Zhang et al., 2022b). As well, isoliquiritigenin has the potential to obstruct β-catenin/ABCG2 signaling via exciting the proteasome destruction pathway (Wang et al., 2014).

The classification of flavonoids

Structurally, flavonoids are divided into six primary groups comprising: Flavonols, flavones, isoflavones, flavanones, flavanols, and anthocyanins (Figure 3).

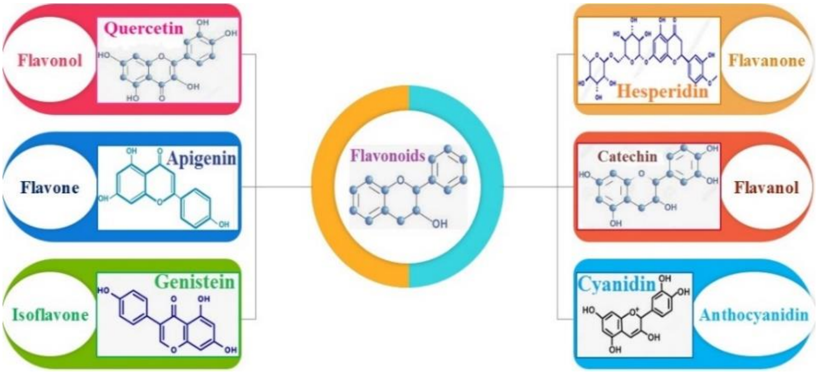

Figure 3: The classification and chemical structure of flavonoids.

Flavonols

Flavonols are among the most prevalent flavonoids found in fruits and green vegetables, and flavones' principal origins include leaves, rinds, barks, and pollens (Niedzwiecki et al., 2016). Onions, curly kale, leeks, broccoli, fresh capers, dried parsley, elderberry juice, rocket lettuce, red onions, cranberries, figs, apples, red wine, and tea are the most plentiful resources of flavonols (Manach et al., 2004).

Flavonols' major elements are quercetin and kaempferol. Quercetin, known as vitamin P, has anticancer properties that include targeting molecular pathways related to glucose metabolism and mitochondrial function, as well as its ability to improve cell viability loss, apoptosis, and autophagy through regulation of the PISK/Akt/mTOR, Wnt/catenin, and MAPK/ERK1/2 pathways (Kaushik et al., 2012; Li et al., 2022). Kaempferol, as a major flavonoid aglycone, has mechanisms of anticancer action that involve apoptosis, cell cycle arrest at the G2/M phase, downregulation of epithelial-mesenchymal transition (EMT)-related markers, and phosphoinositide 3-kinase/protein kinase B signaling pathways (Imran et al., 2019).

Flavones

Flavones are mostly composed of the glycosides luteolin (in rooibos tea) and apigenin (in traditional teas such as black and green) (Spatafora and Tringali, 2012). Flavones function as an effective anticancer agent. In carcinogenesis, flavones regulate signal transduction pathways. Flavones have been shown to modulate cell cycle progression, oxidative stress, angiogenesis, and metastasis, also numerous molecular mechanisms that eventually restrain disease progression (Khan et al., 2021).

Nobiletin, a bioactive polymethoxylated flavone (PMF), is particular to Citrus depressa Hayata (a common citrus fruit) and has a high flavone concentration (Li et al., 2018). Because of its antioxidant and anti-inflammatory qualities, nobiletin has a wide range of biological effects. Investigative results show that nobiletin repressed ERK1/2 activity, caused the cell cycle to stall at the G0/G1 phase, and blocked cyclin-D1 and p21 overexpression. In addition, nobiletin in MDA-MB-468 cells reduced mTOR and AKT activity and induced apoptotic cell death by decreasing Bcl-xL expression without altering Bax levels (Noguchi et al., 2016).

Isoflavone

Isoflavones (daidzein, genistein, and glycitein) are flavonoids with structural similarities to estrogens and the most flavonoids present in soybeans, soy-derived products, and green and mung beans (Terahara, 2015). Genistein, a type of natural phytoestrogen isoflavone found in soybeans, has anti-cancer properties. Further, genistein has been demonstrated to decrease resistance to cancer treatment and inhibit the relapse or recurrence of cancer. Also, Genistein reduced the growth and proliferation of MCF-7 breast cancer cells whilst inducing apoptosis (Chen and Chien, 2019).

Flavanones

Flavanones (naringenin, hesperidin, eriodictyol, taxifolin, didymin, and eriocitrin) are obtained from citrus fruits (e.g., oranges, grapefruit, lemons, and aurantium), grapes, tomatoes, the medicinal herbs of Rutaceae, Rosaceae, Leguminosae, and other aromatic plants like mint (Barreca et al., 2017). Hesperidin, a flavanone glycoside, has anticancer properties owing to its antioxidant and anti-inflammatory characteristics, as well as its capacity to overcome drug resistance in cancer cells. Hesperidin connects with a variety of cellular targets and mechanisms, inhibiting tumor growth by triggering apoptosis and cell cycle arrest, as well as inhibiting tumor cell metastasis and angiogenesis (Aggarwal et al., 2020). In vitro therapy of prostate cancer cells with hesperidin caused a considerable decrease in cell proliferation in a dose-related way. The decrease in cancer cell growth is caused by cell cycle arrest, necrosis-like apoptotic cell death driven by the intracellular buildup of ROS molecules, and a reduction in mitochondrial membrane potential (MMP) (Ning et al., 2020).

Flavanols

Flavanols (also termed flavan-3-ols or catechins) are exist in the form of gallic acid esters or free form in a variety of products, including apples, cherries, plums, apricots, black tea, green tea, dark chocolate, red wine, and notably fruit skins (e.g., apple, grape) (Rothwell et al., 2013). Catechin, as a flavan-3-ol, is the primary bioactive antioxidant ingredient of green tea (*Camellia sinensis*), which is known for its anticancer and anti-inflammatory properties. Catechin and its stereoisomers have been demonstrated to have anti-inflammatory, anti-diabetic, anticancer, antibacterial, neuroprotective, hepatoprotective, and memory-enhancing characteristics, mostly through their influence on the NF-kB, Nrf-2, TLR4/NF-kB, COMT, and MAPK pathways (Baranwal et al., 2022). Green tea catechins have been demonstrated to significantly preclude the risk of lung, breast, esophageal, stomach, liver, and prostate cancer (Musial et al., 2020).

Anthocyanidins

Anthocyanidins (cyanidin, delphinidin) are organic pigments that are present in the cell exterior layer of many edible products, such as blueberries, strawberries, raspberries, red wine, and red onions. They are found in the flowers and fruits of a variety of plants, and they impart red, pink, blue, or violet shades (Khoo et al., 2017). Anthocyanins can hinder the proliferation of cancer cells by regulating the cell cycle at diverse dividing phases with modulating expressions of oncogene, which is assisted by the expression of various cyclins and their partners CDKs and/or CDKIs (Kumar and Pandey, 2013).

Blueberry

Blueberries are an enormous genus of perennial flowering plants that generate blue or purple berries (Figure 4). They are categorized as *Cyanococcus* under the *Vaccinium* genus and family Ericaceae (Saradhi et al., 2022). Blueberries have a high concentration of beneficial chemicals, primarily flavones and other polyphenolic compounds (Zeng et al., 2021b). The major anthocyanins were delphinidin, malvidin, and petunidin glycosides, which accounted for more than 90% of the overall anthocyanin content. Lueberry anthocyanins display a wide range of biological activities, including anticancer activity, antioxidant activity, antibacterial activity, anti-inflammatory activity, and anti-diabetic action (Yang et al., 2022). According to several studies, blueberry anthocyanin can prevent carcinogenesis and tumor cell proliferation by restraining the formation of pro-inflammatory compounds, oxidative stress and its products, including DNA damage, reducing the growth of cancer cells, and enhancing apoptosis (A Johnson and H Arjmandi, 2013). Another investigation demonstrated that blueberry anthocyanins had a suppressive impact on HCT-116 cells, which is mostly connected to the triggering of apoptosis, G0/G1 cell cycle arrest, reactive oxygen species modulation, and declaration of matrix metalloproteinase (Wang et al., 2018).

Figure 4: Flowers and fruit of blueberry (Vaccinium sect. Cyanococcus).

2.4. Anticancer Effect of Stilbenes

Natural stilbenes are another significant type of phytoalexin polyphenol present mainly in grapes, red wine, peanuts, and berries in predominantly glycosylated cis and trans isomeric forms (Teka et al., 2022). Stilbenes have a high potential for cancer inhibition owing to their antioxidant, cell death activation, and anti-inflammatory activities, each of which has minimal toxic effects (Navarro-Orcajada et al., 2022). Resveratrol, piceatannol, and pterostilbenes are the most renowned examples of stilbenes (Zhou et al., 2016).

Resveratrol

Resveratrol (trans-3,4,5-trihydroxystilbene) is a well-studied polyphenol for anticarcinogenic activities in medicinal herbs obtained from *Vitis vinifera* and has been exist in several organic components such as grapes, peanuts, berries, and rhubarb (Bhat and Pezzuto, 2002). Resveratrol has chemotherapy and chemopreventive impacts on a variety of human cancers, including breast, cervical, ovarian, liver, thyroid, prostate, esophagus, stomach, and colon cancers (Rauf et al., 2018). Resveratrol can restrict HT29 and HCT116 cell proliferation by partly upregulating miR-34c to decrease the protein expression of its target stem cell agent. The research also demonstrated that when p53 is activated, cells might amplify this impact by blocking the phosphatidylinositol-3-kinase (P13K)/Akt pathway and sensitizing colon cancer cells to oxaliplatin by controlling miR-34c (Yang et al., 2015). Moreover, resveratrol decreased Sox2 expression as well as the activity of STAT3 and Akt in breast cancer cells induced by CAF-CM (Suh et al., 2018). In addition, piceatannol is a naturally occurring resveratrol analog that upregulates miR-129 expression in HCT-116 and HT-9 cells. Piceatannol also downregulates Bcl-2 protein while upregulating Bax protein after upregulating miR-129, causing cancer cell apoptosis (Zhang et al., 2014).

Pterostilbene

Pterostilbene (PTS), a natural dietary polyphenol obtained from Cyanococcus, is most commonly observed in lueberries. Pterostilbene has the same composition and biological action as resveratrol, but with a longer half-life and great oral bioavailability (Wang and Sang, 2018). According to Wakimoto et al. (Wakimoto et al., 2017), pterostilbene suppressed cell proliferation to the highest level in triple-negative MDA-MB-468 cells. Pterostilbene significantly increased ERK1/2 activation and cyclin D1 suppression, which were followed by overexpression of BAX without affecting BCL-xL and the repression of mTOR and AKT phosphorylation.

2.5. Anticancer Effect of Lignans

Lignans are polyphenolic bioactive compounds with a very high content of antioxidants. Important sources of these compounds are fruits, cruciferous vegetables, flaxseeds, sesame, legumes,algae, pumpkins, brussel sprouts, and seeds of plants (Rodríguez-García et al., 2019). Various research have indicated that the main bioactive effects of lignans are their anticancer activities. Lignans have powerful chemotherapeutic and chemopreventive actions among the phenolic substances, and they will be useful chemotherapeutic drugs in future years (Mukhija et al., 2022). For example, purified flaxseed hydroxylate (PFH) in human breast cancer cell lines (T47D and MCF-7) and mice bearing tumors decreased the expression of the metastasis marker 1-α, metalloproteinases, and VEGF, a significant activator of angiogenesis, and raised caspase-3-dependent apoptosis (Ezzat et al., 2018).

3. ANTICANER ACTIVITIES OF TERPENOIDS

Terpenoids, commonly known as isoprenoids, are the largest class of naturally existing organic chemicals and phytochemicals made up of unsaturated hydrocarbon entities called isoprene units with the basic structure (C5H8)n also their oxygenated, hydrogenated, and dehydrogenated derivatives (Ninkuu et al., 2021). Terpenoids are divided into monoterpenoids, hemiterpenoids, iridoids, sesquiterpenoids, diterpenoids, sesterterpenoids, riterpenoids, and polyterpenoids based on their chemical structure (Adedokun et al., 2023). Terpenoids are the main ingredients of the essential oils generated by fragrant plants and tree resins, including turpentine, and they contribute to the relishes of cinnamon, cloves, and ginger, as well as the yellow and red colors of sunflowers and tomatoes (Webb et al., 2014). Well-known terpenoids involve citral, menthol, camphor, and curcuminoids exist in turmeric and mustard seed (Kamatou et al., 2013). Amid the secondary metabolites of plants, terpenoids include the most chemically and structurally varied class of natural chemicals, wich also includes steroids and carotenoids. Terpenoids isolated from different natural sources possess biological activities, pharmacological activities, anti-cancer, anti-oxidation, anti-viral, and potent anti-inflammatory activities and are utilized for medicine and biotechnology. For instance, the antimalarial medicines Artemisinin and the anticancer medicine paclitaxel (Taxol), vincristine (meroterpenoid), and taxol (diterpenoid) are utilized for cancer therapy and corticating, which has substantial antiangiogenic action and can be effective in the treatment of cancer and macular degeneration (Yang et al., 2020; Padhy et al., 2023). Furthermore, some of the anticancer effects of terpenoid compounds are linked to a reduction in inflammation and oxidative stress. For instance, the tricyclic diterpenoid paclitaxel has been utilized to treat numerous cancers, including breast cancer, ovarian cancer, and non-small-cell lung cancer, by stabilizing microtubules (Hood et al., 2002). Terpenoids also have a significant function in the depolarization of cancer cell membranes. In vitro and in vivo epidemiological assays have proposed the anti-proliferative function of terpenoids in different cancer (Huang et al., 2012). Terpenoid compounds' action mechanism is based on the suppression of tumor cell growth via necrosis, and they also play an important role in the depolarization of cancer cell membranes. Terpenoids have a high potential for controlling miRNAs to induce apoptosis and prevent cancer cell growth. Chemically terpenoid-based supplements contain roughly 40,000 different compounds, representing an unrivaled source of variation in chemicals that have significant anticancer abilities when blended with chemotherapy agents (Ateba et al., 2018).

3.1. The Common Terpenoids in Herbals with Antitumor Activities

The chemical structure and herbal source of common terpenoids with antitumor potential containing cucurbitacin B, ursolic acid, α-santalol, citral, betulinic acid, limonin, paclitaxel, and physalin are shown in (Figure 5).

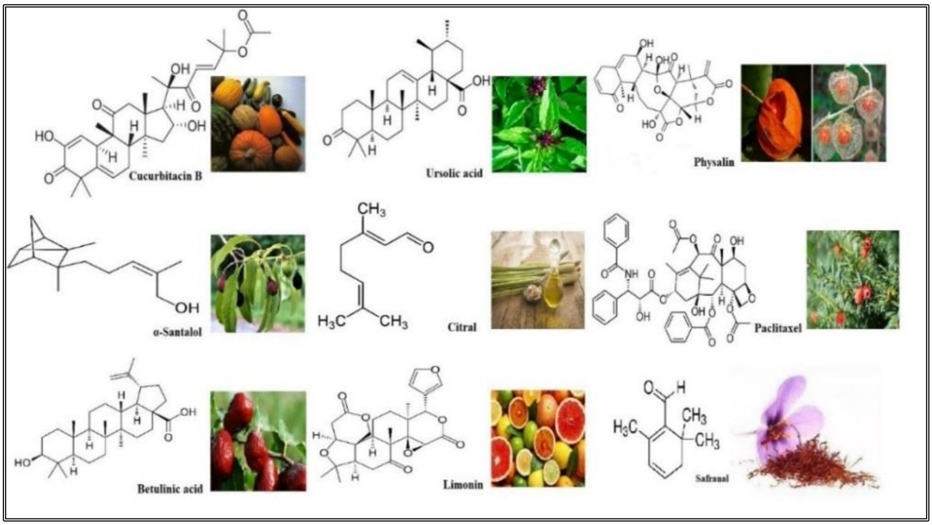

Figure 5: The chemical structure and herbal source of common terpenoids with antitumor potential.

Cucurbitacin B

Cucurbitacin B (Figure 5) is a steroidal tetracyclic terpene derived from the Cucurbitaceae family, including cucumbers, gourds, and pumpkins. Some cucurbitacin’s have been shown to have antiproliferative effects on ovarian

(El-Senduny et al., 2016), pancreatic (Zhou et al., 2017), lung, breast, and brain cancer cell lines (Jayaprakasam et al., 2003). Cucurbitacin B has been demonstrated to inhibit NF-B and the signal transducer and activator of transcription 3 (STAT3), aiding in the induction of apoptosis (Aribi et al., 2013).

Ursolic acid

Ursolic acid (Figure 5), as a pentacyclic triterpene acid, is mostly derived from *Ocimum tenuiflorum* and exists in different fruits and veggies. Ursolic acid suppresses breast cancer cell proliferation via caspase-3 and GSK, which PI3K/AKT modulate via the NF-B signaling pathway (Hanušová et al., 2017). Besides, ursolic acid can enhance the expression of miR-4500 in HCT116 and HT29 cell lines, obstructing colon cancer cell proliferation and extenuating STAT3 activation (Kim et al., 2018).

α-Santalol

α-Santalol (Figure 5), as a sesquiterpene, is obtained from the Santalum. In a variety of cancer forms, the anti-tumor and cancer-avoidance properties of α-santalol have been reported to involve cell death progression through apoptosis and cycle arrest. Also, the restraint of cancer cell migration by α-santalol could be accomplished mostly by blocking the Wnt/-catenin pathway (Bommareddy et al., 2018).

Citral

Citral (Figure 5), as a terpene-based aliphatic aldehyde that is exist mostly in essential oils obtained from citrus, ginger, and lemon, possesses antineoplastic and antiproliferative properties. Citral is a strong suppressor of the aldehyde dehydrogenase-1A3 (ALDH1A3) enzyme, and it has been found to block ALDH1A3-mediated breast tumor growth by impeding the formation of colonies and controlling gene expression (Nigjeh et al., 2018).

Betulinic acid

Betulinic acid (Figure 5) is a lupine-structured pentacyclic triterpene that is mostly derived from white birch bark and wild jujube seeds (Šiman et al., 2016). Betulinic acid prevents breast cancer cell proliferation by blocking the formation of topoisomerase and cyclins, resulting in cell cycle arrest. Betulinic acid suppresses vascular endothelial growth factor (VEGF) signaling and the activation of specificity protein transcription factors and NF-B, resulting in apoptosis through the mitochondrial pathway and anti-angiogenesis. Additionally, betulinic acid restrains the expression of matrix metalloproteases, which have an anti-metastatic effect (Luo et al., 2016).

Limonin

Limonin (Figure 5), as a triterpenoid derived from citrus, can modulate the STAT3/miR-214 signaling cascade to reduce inflammation. Citrus limonoids cause apoptosis and prevent pancreatic cancer cells from proliferating (Murthy et al., 2021), ovarian (Bae et al., 2020), and colon cancer cells (Murthy et al., 2013) . Limonin has been demonstrated to have substantial anti-inflammatory properties in DSS-induced experimental colitis, involving a considerable decrease in the illness's severity index, damage to the intestines, and levels of proinflammatory cytokines (Liu et al., 2019).

Paclitaxel

Paclitaxel (the generic term for taxol) (Figure 5) is a tricyclic diterpenoid combination found in the bark and needles of Taxus brevifolia that has been utilized for the therapy of several cancers, particularly breast cancer, ovarian cancer, and non-small-cell lung cancer, as a microtubule-stabilizing agent (Adedokun et al., 2023; Wani et al., 1971).

Physalin

Physalins (Figure 5), as a triterpene chemical group, are the major significant phytochemical components of *Physalis alkekengi* L. *Physalis alkekengi* L. (bladder cherry, Chinese lantern, Japanese lantern, strawberry groundcherry, or winter cherry) is a valuable medicinal plant of the Solanaceae family known for its various curative characteristics, including anticancer, anti-inflammatory, antimicrobial, antiparasitic, and antiviral. This plant contains a variety of phytochemical components, such as steroids, terpenoids, flavonoids, alkaloids, and vitamin C (Sastry et al., 2019; Mazova et al., 2020). Researchers have shown that the hydroalcoholic extract of P. alkekengi was found to have exceptional potential for the therapy of estrogen-positive breast cancer by increasing the pathway of apoptosis in this cancer type. Physalins are multipurpose compounds that function in various pathways of cell signaling and induce mechanisms of cell death or immunomodulation (Meira et al., 2022). According to research, physalins can help prevent cancer cell development by arresting the cells at the G2/M phase of the cell cycle. Actually, physalins exercise their impact by decreasing the expression and activity of cyclines A and B, as well as the activity of Cdc2, and increasing the phosphorylation of Cdc2 (Bahmani et al., 2016).

Safranal extract

Crocus sativus L., also referred to as saffron crocus, is a flowering plant in the Iridaceae family (Mzabri et al., 2019). The stigma of this plant is utilized to make saffron or red gold. Crocetin, crocins, picrocrocin, and safranal (Figure 5) are the four major bioactive constituents of saffron stigma (Winterhalter and Straubinger, 2000) . The aroma is caused by safranal (a monoterpene aldehyde), the essential oil's major component (de Castro and Quiles-Zafra, 2020). Several research have shown that saffron and its major components have anticancer and cancer-preventive properties (Mousavi et al., 2014).

4. ANTICANCER ACTIVITIES OF ALKALOIDS

Alkaloids are recognized as a varied class of nitrogen-comprising naturally bioactive substances that may include one or more nitrogen atoms inside a heterocyclic ring (Marchant et al., 2018). The distribution of alkaloids is found mainly to be in higher plants, like those attributed to Ranunculaceae, Leguminosae, Papaveraceae, Menispermaceae, and Loganiaceae (Jing et al., 2014). The content of alkaloids in parts of plants differs according to the plant. The greatest amounts are found in the leaves of black henbane, the fruits or seeds of strychnine, the roots of *Rauvolfia serpentina*, and the back of cinnamon (Komarova and Tolkachev, 2001). Alkaloids, as one of the greatest classes of plant secondary metabolites, are engaged in the plant defensive system and are particularly effective in this regard owing to their toxicity, and alkaloids natural products possess diverse therapeutic effects. Some of these combinations, including camptothecin and vinblastine, have been developed into chemotherapeutic medications, and others, such as vincristine, berberine, and vinblastine, have been found to be effective sources for the identification of cytotoxic agents as anticancer agents (Lu et al., 2012).

In terms of history, Charles Beer and Robert Noble identified the first kind of alkaloid used in cancer therapy by accident in the 1950s from *Vinca rosea* (Banyal et al., 2023). Alkaloids, by precluding the constitution of microtubules, induce cell cycle arrest at the metaphase phase and therefore could prevent cancer (Asadi-Samani et al., 2016). Alkaloids considerably increased human cancer cell line sensitivity to multiple drug resistances (Wang et al., 2013). In fact, various targets are involved in the mechanism of these substances, including anti-angiogenesis, apoptosis, autophagy, cell cycle arrest, differentiation, anti-multidrug resistance (anti-MDR), chemoprevention, and anti-metastasis (Lu et al., 2012). Furthermore, alkaloids have several distinct chemical properties, which make them appealing possibilities for utilize in medical. Alkaloids in their primitive state are soluble in acidic situations but become lipid membrane penetrable when neutral after missing their protons (Heinrich et al., 2021). Due to these qualities, alkaloids have been utilized in a variety of applications in plant and human illness therapy. Some of these combinations, such as vinblastine, camptothecin (CPT), a well-known topoisomerase I (TopI) inhibitor (Huang et al., 2007), and vinblastine, which interacts with tubulin, have previously been effectively developed into chemotherapeutic medicines (Mir et al., 2023).

The naturally acquired alkaloids like berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine that show anticancer, anti-proliferative, and anti-metastasis characteristics against diverse cancers and have received substantially more anticancer investigations were chosen for study. The investigation of anticancer alkaloids varies greatly. Some concentrate on cancer prevention, whereas others concentrate on cancer chemotherapy, particularly the assessment of antiproliferative activity.

4.1. The Common Alkaloids In Herbals With Anticancer Activities

The anticancer activity and the mechanisms involved in suppression of cancer for common alkaloids including berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine are summarized in (Figure 6).

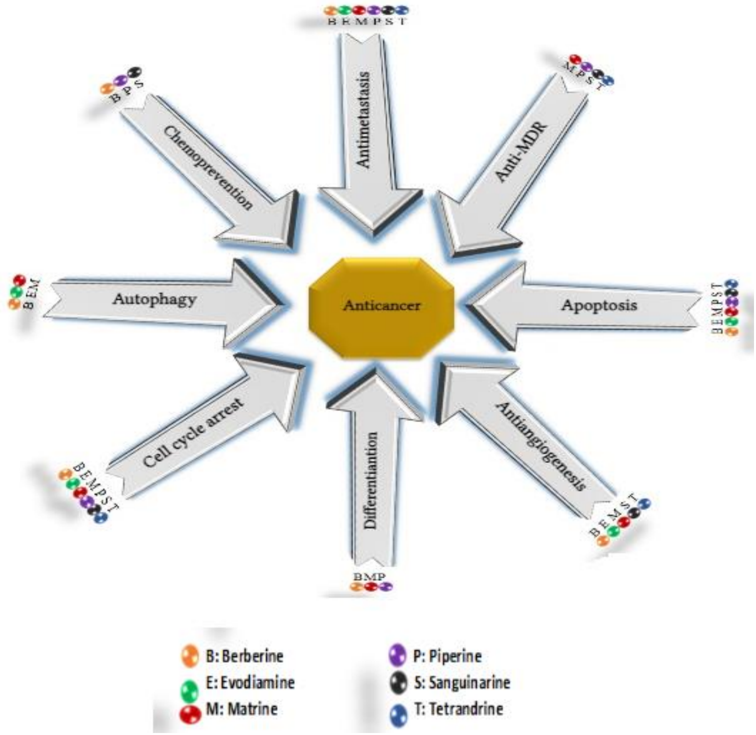

Figure 6: Multiple inhibition mechanisms of berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine to suppress various type of cancer.

Berberine

Berberine (Figure 6), a kind of chemical molecule known as an alkaloid, is an isoquia found in many natural plants, including Rhizoma coptidis Numerous investigations have demonstrated that berberine has antitumor properties in multiple aspects of carcinogenesis and cancer development at eighter *in-vitro* and *in-vivo* assays (V Diogo et al., 2011). In a study, it was shown that berberine be able to boost the expression of Integrin b4 and programmed cell death 4 proteins in the human colon cancer HCT116 cell line by blocking miR-21 and promoting cancer cell lines apoptosis (Lü et al., 2018). Berberine's other mechanisms are mostly connected to its influence on apoptosis and cell cycle arrest, such as modulation of the cyclin-dependent kinase (CDK) family of proteins (Mantena et al., 2006) and expression modulation of the B-cell lymphoma 2 (Bcl2) family of proteins (such as Bax, Bcl-2, and Bcl-xL) family of proteins (Eom et al., 2010), as well as caspases (Mantena et al., 2006). Berberine also inhibited the growth of many cancer cell lines by causing cell cycle arrest in G1 or G2, as well as apoptosis (Huang et al., 2007). Moreover, the nuclear factor-light chain enhancer activation of activated B cells (NF-B) is prevented by berberine and triggers the formation of intracellular reactive oxygen species in cancer cells (Sun et al., 2009).

Evodiamine

Evodiamine (Figure 6), as a quinolone alkaloid, comprises among the most important biologically active substances obtained from *Evodia rutaecarpa* (Shin et al., 2007). In a some of cancer cell lines, evodiamine shows anticancer activities either *in-vivo* and *in-vitro* by triggering apoptosis or cell cycle arrest, suppressing invasion and angiogenesis, and inhibiting tumor growth and metastasis (Shyu et al., 2006). Evodiamine similarly promotes autophagy, which is a survival mechanism (Yang et al., 2008). When exposed to evodiamine, intracellular ROS levels rapidly rise, followed by the commencement of mitochondrial depolarization. The production of ROS and nitric oxide works in tandem to cause mitochondria-dependent apoptosis (Yang et al., 2007). In certain cancer cells, evodiamine triggers caspase-dependent/independent apoptosis, decreases Bcl-2 expression, and stimulates Bax expression (Lee et al., 2006). The phosphatidylinositol 3-kinase/Akt/caspase and Fas ligand (Fas-L)/NF-κB signaling pathways may be involved in evodiamine-caused cellular dying (Wang et al., 2010).

Matrine

Matrine (Figure 6) is an important alkaloid that exists in a variation of Sophora plants, notably *Sophora flavescens* Ait (Lai et al., 2003). It has numerous pharmacological activities, as well as antibacterial, antiviral, antiinflammatory, antiasthmatic, and anticancer characteristics (Zhang et al., 2011). Matrine inhibits the growth of various cancer cells, primarily by triggering G1 cell cycle arrest or apoptosis (Liu et al., 2010). Matrine has the capability to initiate both apoptosis and autophagy in human cancer cells, including hepatoma G2 cells and SGC7901 cells (Zhang et al., 2010). Matrine likewise stimulates K562 differentiated cells and offers antiangiogenesis properties (Zhang et al., 2001). Numerous proteins associated with apoptosis or cell proliferation, like E2F-1, Bax, Bcl-2, Fas, and Fas-L, are affected by matrine (Dai et al., 2009; Zhang et al., 2008). It partly prevents cancer cell invasion by suppressing MMP-2 and MMP-9 production and regulating the NF-B signaling pathway (Yu et al., 2009).

Piperine

Piperine (Figure 6), as a piperidine alkaloid extracted from Piper nigrum and Piper longum, is a substance present in a number of spices (Szallasi, 2005). It has antioxidant, anti-inflammatory, antimutagenic, and tumor-inhibiting properties (Bae et al., 2010). According to research, piperine caused apoptosis, raised the proportion of cells in the G2/M phase in 4T1 cells, and prompted K562 cells to develop into macrophages and monocytes (Lai et al., 2012; Song et al., 2008). Piperine also possesses potent antimetastatic activity toward B16F-10 melanoma cell-induced lung metastasis (Pradeep and Kuttan, 2002). Extremely, piperine additionally blocks the activities of P-glycoprotein and CYP3A4 (one of the primary docetaxel metabolizing enzymes), that is not just impacts drug metabolism it also triggers a resensitization of MDR cancer cells (Pradeep and Kuttan, 2002; Li et al., 2011a).

Sanguinarine

Sanguinarine (Figure 6) which is a benzophenanthridine alkaloid, comes from the Papaveracea family, which contains the plants *Sanguinaria canadensis* L. and *Chelidonium majus* L. (Mahady and Beecher, 1994). Sanguinarine possesses antibacterial, antifungal, and anti-inflammatory activities, as well as anticancer potential, and is presently attracting attention from scholars (Hussain et al., 2007). It causes cell cycle arrest at various stages or apoptosis in a number of cancer cells (Adhami et al., 2004). Sanguinarine significantly increases the sensitivity of breast cancer cells to ligand-mediated apoptosis-inducing tumor necrosis factor (TNF) (Kim et al., 2008). It has antiangiogenic properties and overpowers the P-glycoprotein-mediated MDR phenotype (Weerasinghe et al., 2006). Sanguinarine is an effective inhibitor of MKP-1, a mitogen-activated protein kinase phosphatase that is overexpressed in a number of tumor cells (Vogt et al., 2005). NF- B activation triggered by TNF, interleukin-1, phorbol ester, and okadaic acid can be suppressed by sanguinarine in a potent manner (Chaturvedi et al., 1997). It also effectively blocks STAT-3 activation (Sun et al., 2012); reduces the levels of CDKs, cyclins, MMP-2, and MMP-9 (Choi et al., 2009); upregulates p21and p27 (Adhami et al., 2004), and the phosphorylation of p53; triggers caspases and raises the level of death receptor 5 (Hussain et al., 2007).

Tetrandrine

Tetrandrine (Figure 6), as a bisbenzylisoquinoline alkaloid derived from the root of *Stephania tetrandra*, has a variety of therapeutic effects, that is immunomodulatory, anti-inflammatory, and anticancer properties (Li et al., 2001). Tetrandrine inhibits angiogenesis, promotes apoptosis, and causes various stages of cell cycle arrest in a range of human cancer cells (Ng et al., 2006), such as leukemia, bladder, colon, hepatoma, and lung (Li et al., 2011b). Tetrandrine additionally, in effect, promotes p27, p21, p53, and Fas (Li Chen et al., 2008); inhibits Akt phosphorylation, CDKs, and cyclins (Cho et al., 2009); modifies Bcl-2 family members including Bax, Bcl-xL, and activates caspases (Oh and Lee, 2003). By blocking P-glycoprotein, tetrandrine makes MDR cancer cells more sensitive to doxorubicin, paclitaxel, docetaxel, and vincristine (Fu et al., 2004). Thus, tetradrine presents a huge possibility to treat P-glycoprotein-mediated MDR malignancies as an MDR modulator. Tetrandrine appears to be a good option for combining several chemotherapeutic treatment drugs, such cisplatin and 5-fluorouracil, whether *in-vitro* or *in-vivo*. Thus, tetradrine could be utilized as a supplement to cancer chemotherapy or radiation (He et al., 2011).

5. CONCLUSIONS

Because of evolving lifestyle conventions and growing industrialization, the probability of developing cancer is anticipated to increase in the years to come. Notwithstanding the efficacy of the known therapies for cancer treatment, the unfavorable side effects of the current anticancer medications necessitate a constant quest for new treatment compounds, notably from herbal sources. In this context, the phytochemicals of organic basis have proven to be useful resources for anticancer agents. There is a requirement to find more of these organic compounds that offer better activity with reduced toxicity compared to the presently endorsed synthetic anticancer medicines.

Overall, more research should be carried out to investigate and identify other pharmacokinetic properties of plant-derived compounds, and then make them suitable for application in cancer treatment. These outcomes will assist investigators in identifying the compounds derived from herbs that could be tested in pre-clinical and clinical investigations of anticancer therapies.

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CHAPTER 6

FLAVONOIDS

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INTRODUCTION

Among the antioxidant compounds we get from our diet, the main ones of plant origin are polyphenolic compounds. The main nutritional foods are apples, strawberries, grapes, and cherries, and they contain up to 200-300 mg of polyphenols per 100 g of fresh weight. The two primary types of polyphenols are flavonoids and phenolic acids (Scalbert et al., 2005).

Flavonoids, a word of Latin origin, are secondary metabolites known in plants derived from the Latin word yellow. Flavonoids are compounds with low molecular weight in plants. When we say flavonoids, we are talking about the compounds that make up the colored parts of plants such as colorful vegetables and fruits. They are compounds that form colored parts such as yellow, red, blue, and purple (Procházková et al., 2011). Some studies initially show flavonoids were called "vitamin P" (Pal and Verma, 2013). These compounds are classified in various ways. Many physiological properties have been described in flavonoids (Procházková et al., 2011). Today, they are used in many in vitro and in vivo studies, especially toxicological studies, regarding their pharmacological roles (Bas et al., 2021; Apaydın et al., 2023). It has an essential place among human nutrients such as tea, propolis, and seeds with its health benefits (Cushnie et al., 2005).

Flavonoids, which are considered an important part of human nutritional resources, are a large group of phenolic compounds and especially found in plants that perform photosynthesis. When flavonoids are taken into the body, they are absorbed from the intestines. Absorption may vary depending on the glycoside or aglycane structure of the flavonoid. Many flavonoids, except catechins, are found in plants bound to sugars as b-glycosides. While those in the glycoside form must first be converted to the aglycan form, aglycans are absorbed directly. Following absorption in the intestines, they are conjugated or metabolized to metabolites phenolic compounds in the liver by methylation, sulfation, or glucuronidation (Kumar and Pandey, 2013). We see these secondary metabolites in the plant kingdom's angiosperm, primarily flower pigment groups (Panche et al., 2016).

Today, many diseases are associated with free radical damage. Therefore, compounds that eliminate this damage or improve its effect are known as antioxidants. We can say that studies have mostly emphasized the antioxidant properties of flavonoids. In addition to therapeutic effects of flavonoids have many important properties such as antioxidant (Uzunbayır and Apaydın, 2021), anti-microbial (Cushnie et al., 2005), anti-inflammatory (Maleki et al., 2019), anti-mutagenic (Matsumoto et al., 2017), anti-ischemic (Chu et al., 2007), antiviral (Badshah et al., 2021), anticancer (Leon-Gonzales et al., 2015) and immunopharmacological properties (Ielpo et al., 2000). While achieving these properties, flavonoids benefit from their different chemical structures and physiological roles (Panche et al., 2016).

Flavonoids are the most common and numerous group of natural antioxidants that prevent lipid oxidation in biological membranes. Found in fruits, vegetables, nuts, seeds, grains, bark, flowers, and tea (Renugadevi, 2009).

Flavonoids also perform many essential functions in the plants they are found in. For example, we can list protection from UV rays, drought resistance, frost resistance, defense against environmental stress, and protection against harmful compounds found in the soil (Treutter D, 2006).

There are many pathways by which flavonoids inhibit and effect on the viruses. They provide many mechanisms against the toxic effects of viruses. These include preventing the genetic material of viruses from multiplying and stopping protein synthesis at different stages. Additionally, they can prevent viruses from entering the host cell (Badshah et al., 2021).

1. GENERAL PROPERTIES OF FLANONOIDS

It is estimated that the number is over 5000. They are abundant in apples, onions, legumes, cereals, tomatoes, fruits such as citrus, and wine (Ielpo, 2000; Kahraman et al., 2002; Badshah et al., 2021). First, we can classify it as flavanols, flavanones, flavones, isoflavones, flavonols, and anthocyanidins. The difference between flavonoid classes is due to the difference in C carbons, within a class differ in the pattern of substitution of the A and B rings (Pietta, 2000; Kumar and Pandey, 2013; Panche et al., 2016). The nuclear structure of the functional groups of flavonoids is very important in their antioxidant properties (Kumar and Pandey, 2013). Figure 1 shows the general structure of a flavonoid.

When we look at the mechanisms of antioxidant action, the synthesis of enzymes involved in the formation of free radicals can be stopped, or they can suppress these free radicals by chelating trace elements after their formation and upregulation or synthesis of antioxidant defenses (Kumar and Pandey, 2013).

Antioxidants are compounds that cleanse the cells of harmful reactive species. If there is an imbalance between reactive oxygen species and antioxidant species in the cell, a condition called oxidative stress occurs. Oxidative stress is also associated with many diseases such as neurodegenerative diseases, aging, cancer, and ischemia. Flavonoids, vitamins, and other antioxidant compounds reduce the risk of these diseases (Pal and Verma, 2013).

Antioxidants are divided into two groups enzymatic and non-enzymatic antioxidants. Enzymatic antioxidants include SOD (superoxide dismutase), catalase, GST (glutathione-S-transferase), and glutathione reductase. Non-enzymatic antioxidants include minerals such as zinc and selenium, vitamins, and low molecular weight compounds such as glutathione, uric acid, and polyphenols (Bilaloğlu and Harmandar, 1999).

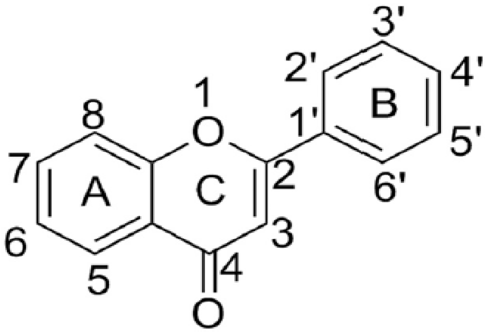

Figure 1: General structure of flavonoid (Badshah et al., 2021).

2. SUBCLASSES OF FLAVONOIDS AND SKELETON STRUCTURES OF FLAVONOIDS

The subclasses of flavonoids include six main subgroups:

- chalcones,
- flavones,
- flavonols,
- flavanones,
- anthocyanins,

- isoflavones (Zhang et al., 2021).

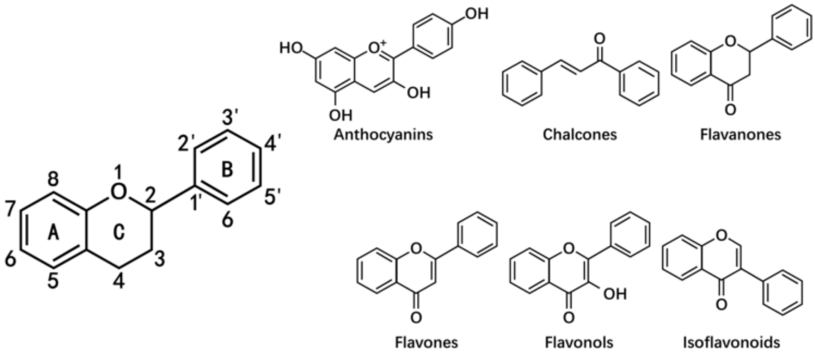

Figure 2: Six main subgroups of flavonoids (Zhang et al., 2021).

2.1 Chalcones

Chalcones contain the “1,3-diarylprop-2-en-1-one” skeleton. The most distinctive feature of chalcones is the presence of the olefinyl bond and keto group in the propane chain (Sulpizio et al., 2018). The structure of a chalcone is shown in Figure 3. The class of flavonoids that do not have a heterocyclic C ring are chalcones and dihydrochalcones. Chalcones are abundant in various fruits and vegetables such as strawberries, pears, and tomatoes. Chalcone and its derivatives have very important biological functions. Chalcones also have subclasses: phloretin, phloridzin, arbutin, and chalconaringenin (Panche et al., 2016). Chalcones and their synthetic derivatives have a broad spectrum of bioactivity, including anti-hypertensive, anti-diabetic, anti-retroviral, anti-histamine, anti-inflammatory, anti-oxidant, anti-ulcer, and anti-cancer. There are many studies in the literature to investigate the biological properties of chalcone derivatives (Ertürk et al., 2023).

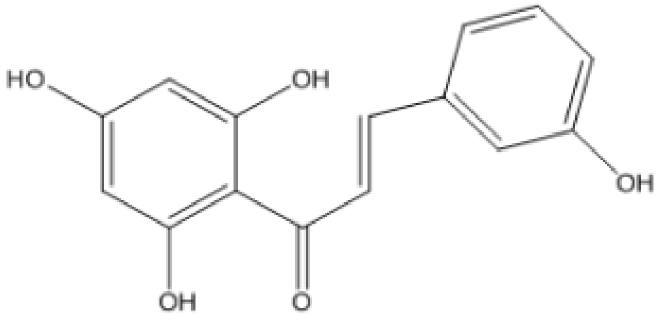

Figure 3: Structure of chalcone (Pal and Verma, 2013)

2.2. Flavone

Flavones are found in many fruits as glycosides, including parsley, celery, mint, red peppers, ginkgo biloba, and chamomile. Flavones have subclasses such as luteolin, apigenin, and tangeritin. They have a double bond between positions 2 and 3 and a ketone in position 4 of the C ring. Especially, the peels of citrus fruits are rich in the polymethoxylated flavones, tageretin, nobiletin, and sinensetin (Panche et al., 2016). The structure of a flavone is shown in Figure 4.

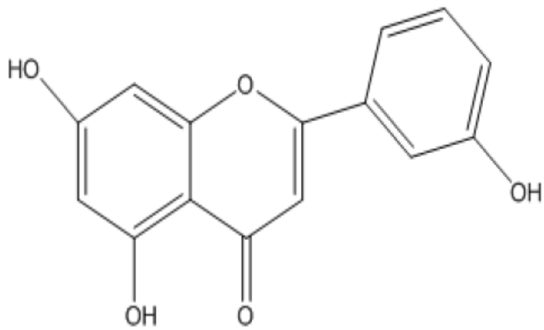

Figure 4: Structure of flavone (Pal and Verma, 2013)

2.3. Flavonol

These flavonoids are containing ketone groups. Lettuce, tomatoes, onions, cabbage, apples, and grapes can be given as examples of this group, whose chemical structure is shown in Figure 5. Quercetin, myricetin, rutin, morin, and kaempferol are flavonols in this class whose antioxidant properties are well-known today (Panche et al., 2016). Flavonols (quercetin, myricetin, and kaempherol) have more antioxidant activity with a structure that allows them to have more effective antioxidant activity than that of anthocyanins (Zheng et al., 2003).

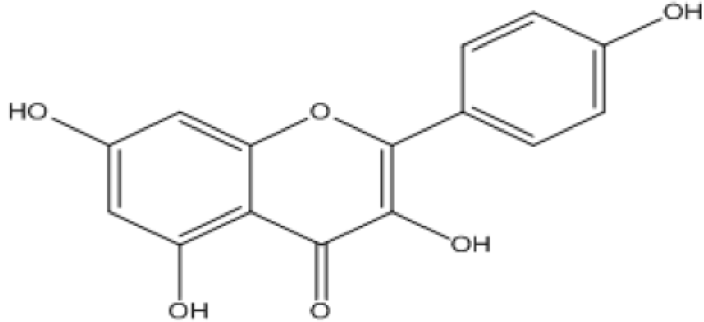

Figure 5: Structure of flavonol (Pal and Verma, 2013)

Quercetin is found in a variety of fruits, vegetables, beverages, nuts, seeds, flowers, and tree bark. It is considered the main antioxidant flavonol in the human diet, especially since it is found in onions (0.3 mg/g) and tea (10-25 mg/L). Therefore, quercetin is the most studied disease with anticancer properties known to date. It is one of the phenolic compounds (Tripoli et al. 2007).

In particular, quercetin functions more in scavenging reactive oxygen species compared to other flavonoids. This antioxidant potential has been attributed to the presence of two pharmacophores, including the catechol group in the B ring and, in particular, the hydroxyl group in the B rings. Additionally, quercetin can modulate the Nrf2-ARE pathway and subsequently eliminate oxidative stress by increasing the synthesis of antioxidant enzymes (Bagheri et al., 2021).

Besides, the protective effects of quercetin as a preventive and therapeutic agent have been studied in oral health care, such as periodontal disease, dental caries, gingivitis, plaque, oral cancer with anti-inflammatory effects against oral pathogens (Bagheri et al., 2021).

2.4. Flavanone

Examples of flavonoids in this group include eriodictyol, hesperidin, and naringenin. They are commonly found in foods such as lemons, grapes, and oranges. The antioxidant properties of flavonoids are due to their free radical scavenging effects. These compounds especially are what give citrus fruits their bitter taste (Panche et al., 2016). As a result of mechanical damage to these parts during juice extraction and heating applied at other stages of processing, more or less naringin may pass into the fruit juice (Puri and Banerjee, 2000).

For example, naringenin is a flavanone that has attracted a lot of attention in recent years and is available in two different forms: glycositic and aglycol (Moghaddam et al., 2020). The protection of naringenin on heart tissue is being studied a lots of studies today (Moghaddam et al., 2020).

Naringenin has been accepted as a potential antioxidant pharmacologically, and its anticarcinogenic, anti-inflammatory, antiatherogenic, antimutagenic, hepatoprotective, and nephroprotective activities have been reported (Erişir et al., 2018).

It has been proven that Naringenin reduces oxidants in the environment in tissue damage caused by various xenobiotics. Researchers reported that naringenin changes SOD, CAT, GPx, and GST (Glutathione S-transferase) activities in rats exposed to chemicals and prevents cell death against ROS in the environment through its antioxidant structure (Erişir et al., 2018).

Researchers reported that naringin blocks H_2O_2-induced cytotoxicity and apoptosis and thus protects normal cells from oxidative damages, but in tumor effect cells, apoptosis is the major mechanism of cancer suppression (Tripoli et al. 2007). The structure of a flavanone is shown in Figure 6.

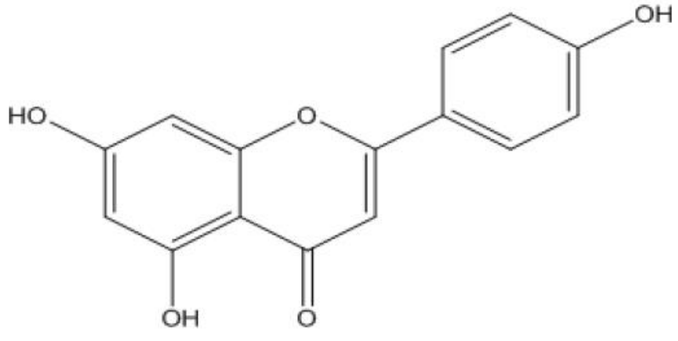

Figure 6: Structure of flavanone (Pal and Verma, 2013)

2.5. Anthocyanins

The antioxidant effect of anthocyanins depends on their ability to bind proteins and chelate metal ions. The antioxidant activities of anthocyanins are closely related to their structures. Anthocyanidins, which form the aglycone part of anthocyanins, and the location and number of sugar groups attached affect antioxidant activity. The plus of the number of -OH in the structure is the o-dihydroxy structure in ring B. Especially 3',4’ positions of B ring are very important to the anti-oxidative role. The binding of -OHs to carbon increases antioxidant activity (Kong et al., 2003; Zheng et al., 2003).

The structure of anthocyanin is shown in Figure 7. Cyanidin, delphinidin, malvidin, pelargonidin, and peonidin are the most commonly studied anthocyanins (Panche et al., 2016). It is a compound that has many health benefits. It is found abundantly in herbal sources such as strawberries, merlot grapes, raspberries, blueberry, cranberry, lingonberry, red grapes, and chokeberry (Zheng et al., 2003).

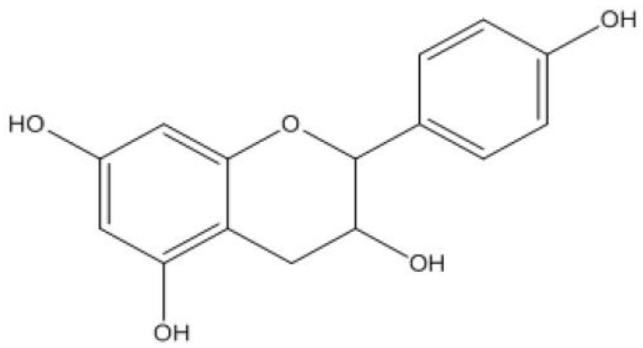

Figure 7: Structure of anthocyanins (Pal and Verma, 2013)

2.6. Isoflavonoids

There are subclasses such as genistin, genistein, daidzein, glycitein, daidzin. They are mainly found in legumes and various medicinal plants. Isoflavones such as genistein and daidzein are known as phytoestrogens and show estrogenic activity in multiple animals (Panche et al., 2016).

Plant-derived estrogens or compounds that have estrogen-like effects are called “phytoestrogens”. While it is more associated with menopause or osteoporosis with its estrogenic and antiestrogenic properties, it has been reported to be associated with cancer with its antioxidant properties. There are three isoflavones in soybeans and soy products that have the most phyto-estrogenic effects. These; daidzein, genistein and glycitein. In the body, genistein is one-third as effective as estrogen when it interacts with the estrogen receptor beta. Genistein produces estrogen-like effects in breast, ovary, endometrium, prostate, vascular, and bone tissues (İnanç and Tuna, 2005). The structure of isoflavonoids is shown in Figure 8.

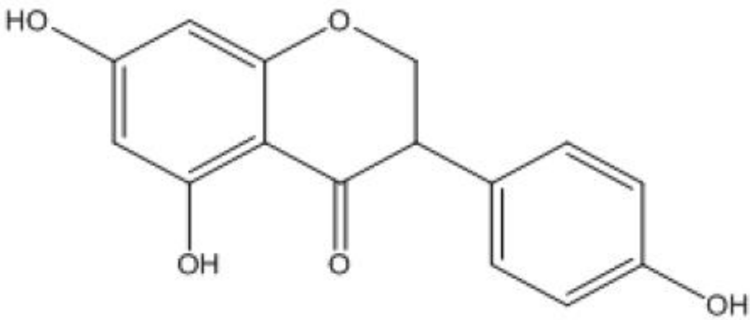

Figure 8: Structure of isoflavonoids (Pal and Verma, 2013)

3. MECHANISMS OF FLAVONOIDS

1. Flavonoids scavenge superoxide radical ($0_2^{-\cdot}$), hydroxyl radical ($^{\cdot}$OH), and singlet oxygen.
2. Flavonoids capture peroxyl radical (ROO$^{\cdot}$) and alkoxyl radical (RO$^{\cdot}$), and break down the lipid peroxyl (LOO$^{\cdot}$) chain.
3. Inhibits cyclooxygenase and lipoxygenase enzymes
4. Chelates transition metals such as iron and copper (Kahraman et al., 2002).

One of the most common effects of cellular damage is lipid peroxidation. It has been reported that flavonoids show protective mechanisms on lipids through various mechanisms (Kumar and Pandey, 2013). Lipid peroxidation is one of the main processes of oxidative damage, which plays a critical role in the toxicity of many xenobiotics. It is well known that levels of Malondialdehyde (MDA), a major oxidation product of peroxidized polyunsaturated fatty acids, have been considered an essential indicator of lipid peroxidation (Uzun and Kalender, 2013).

Previous studies researchers reported that flavonoids like quercetin and catechin can decrease MDA levels induced by toxic materials in experimental animals (Uzun and Kalender, 2013). These ameliorative effects may be due to their higher diffusion into the membranes allowing them to scavenge free radicals (Uzun and Kalender, 2013).

Researchers reported that a possible therapeutic mechanism for the protective activity of flavonoids is their ability to stabilize cell membranes by decreasing membrane fluidity (Uzun and Kalender, 2013).

Studies conducted in recent years have mostly emphasized the antioxidant properties of flavonoids. This section will briefly explain the effects of various flavonoids on experimental animals because dietary flavonoids may display their first antioxidant defense in the digestive tract, by limiting ROS (reactive oxygen species) formation and scavenging them (Pietta, 2000).

The antioxidant activity of flavonoids is due to the arrangement of functional groups related to the nuclear structure. The configuration, substitution, and total number of hydroxyl groups substantially effect many mechanisms of anti-oxidative capacity, such as radical scavenging and metal ion chelation properties (Kumar and Pandey, 2013). Oxidative stress can also have toxic effects on many biological molecules, and proteins and DNA molecules are significant targets of tissue defects (Panche et al., 2016).

Although many studies have shown the healing and protective effects of flavonoids in medicine, it is also emphasized that they have a protective potential against cellular damage caused by various xenobiotic, as seen in Table 1.

Table 1: Some dietary flavonoids and exp erimental studies

Flavonoid	**Experimental model**	**Administered dose**	**Flavonoids affect**	**References**
Catechin and Quercetin	In vivo During 28 days, oral ways to rats	Catechin (20 mg/kg bw) Quercetin (20 mg/kg bw)	Flavonoids have been reported to exhibit potent anti-oxidative and free radical scavenging activities in lung tissues. They are also ameliorated histopathological effects by pesticide	Uzun et al., 2010

			exposure. Catechin and quercetin also had improving effects on oxidative stress parameters.	
Ferulic acid	In vivo During 28 days, oral ways to rats	30 mg/kg bw	Taking ferulic acid protective effects in testicular dysfunction. It could be suggested that the supplementation with ferulic acid may be a potential therapy in the treatment of subchronic dimethoate intoxication	Uzunbayır and Apaydın, 2021
Curcumin And Quercetin	In vivo During 28 days, oral ways to rats	100 mg/kg bw and 50 mg/kg bw, respectively	Quercetin and/ or curcumin supplementation with fipronil significantly protected fipronil-induced changes in kidney function markers such as blood urea nitrogen, creatinine, and uric acid levels, antioxidant enzyme activities, lipid peroxidation, and pathological situations.	Uzunhisarcıklı et al., 2023

Taurine and Curcumin	In vivo During 28 days, oral ways to rats	100 mg/kg bw and 100 mg/kg bw, respectively	Taurine and curcumin treatment with the Bisphenol-A treated group showed ameliorative effects on the rat testes. Phenolic compounds caused a decrease in histopathological findings and an improvement in oxidative stress parameters in testicular tissue.	Kalender et al., 2019
Gallic acid	In vivo During 28 days, oral ways to rats	50 mg/kg bw	Gallic acid caused ameliorative effects on the level of antioxidant enzyme changes and lipid peroxidation caused by pesticide application in the heart tissue of experimental animals.	Calik and Apaydın, 2022

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CHAPTER 7

BIOINSECTICIDE POTENTIALS OF PLANTS

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INTRODUCTION

Since human beings began to engage in agriculture, they have tried to combat creatures that harm agricultural products. They tried to obtain more and higher quality products by increasing agricultural production and fighting against harmful animals. Regarding these studies, they have started to achieve this with chemical drugs for several hundred years. Due to the harmful effects of chemical drugs on humans and other animals, they tend to fight this by natural means. Based on this point, organic bioinsecticide research has emerged very recently and continues rapidly. A lot of research on this continues to be done around the world. Here, the use of plants as bioinsecticides and the effects of which plants are tried to be revealed. For this purpose, n-hexane, methanol and water extracts of different parts of plants were generally used and the bioinsecticide effects of each were tried to be revealed separately. Below are the important findings of some of the many studies on this subject.

In a study conducted in Korea (2003);

Methanol extracts from 30 aromatic medicinal plant species and five essential oils were tested for their insecticidal activities against adults of *Sitophilus oryzae* (L.) and *Callosobruchus chinensis* (L.), using direct contact application and fumigation methods. Responses varied with plant material, insect species, and exposure time. In a test with a filter paper diffusion method at 3.5 mg/cm^2, potent insecticidal activity against both species was produced by an extract from *Cinnamomum cassia* bark, cinnamon (*C. cassia*) oil, horseradish (*Cocholeria aroracia*) oil, and mustard (*Brassica juncea*) oil within 1 day after treatment. Over 90% mortality at 3 or 4 days after treatment was achieved using extracts of *Acorus calamus* var. *angustatus* rhizome, *Acorus gramineus* rhizome, *Illicium verum* fruit, and *Foeniculum vulgare* fruit. An extract from *Cinnamomum sieboldii* root bark gave 100% mortality at 2 days after treatment. At 0.7 mg/cm^2, extracts from *C. cassia, C. sieboldii*, and *F. vulgare* as well as cinnamon oil, horseradish oil and mustard oil were highly effective against both species. In a fumigation test with *S. oryzae* adults, the oils described were much more effective in closed containers than in open ones, indicating that the insecticidal activity of the oils was attributable to fumigant action. The plant extracts and essential oils described could be useful for managing field populations of *S. oryzae* and *C. chinensis* (S.-I. Kim et al. 2003).

In a study conducted in Argentina (2000);

The insecticidal activity of 11 extracts from nine South American medicinal plants has been studied using the *Aedes aegypti* larvicidal assay. Eight of the 11 plant extracts studied showed toxicity against the *A. aegypti* larvae (LC_{50} <500 μg/ml). The dichloromethane extracts of *Abuta grandifolia* and *Minthostachys setosa* demonstrated high larvicidal activity, the most active being the dichloromethane extract of *A. grandifolia*, with an LC_{50} =2.6 μg/ml (LC_{100} = 8.1 μg/ml), indicating an activity 2-fold higher than β-asarone, a natural botanical insecticide used as a positive control (LC_{100} =16 μg/ml). On the other hand, the dichloromethane extract of *M. setosa* was quite potent against *A. aegypti* larvae showing an LC_{50} =9.2 μg/ml (LC_{100} =25.2 μg/ml). The results obtained suggest that the extracts of *A. grandifolia* and *M. setosa* are promising as larvicides against *A. aegypti* larvae and could be useful in the search for new larvicidal natural compounds (Ciccia, G. Et al. 2000).

In a study conducted in Morocco (2006);

Methanol extracts from four medicinal plants, *Peganum harmala* (Zygophyllaceae), *Ajuga iva* (Labiateae*),* *Aristolochia baetica* (Aristolochiaceae) and *Raphanus raphanistrum* (Brassicaceae) were studied for their insecticidal effects on the stored grain pest *Tribolium castaneum* (Herbst). Response varied with plant species. Larvae growth was significantly inhibited when they were fed with extracts incorporated into the diet. Good insecticidal activity against *T. castaneum* larvae and adults was achieved with extract of *P. harmala* seeds, followed by extract of *A. iva*, *Ari. baetica* and *R. raphanistrum* aerial parts. The extracts of the four plants disrupted the developmental cycle of the insect. Extracts of *P. harmala*, *A. iva* and *Ari. baetica* inhibited F1 progeny production. These naturally occurring plant extracts could be useful for managing populations of *T. castaneum* (Jbilou, R. et al. 2006).

In a study conducted in Turkey (2011);

In this research, the hexane extracts of the aerial parts of four *Salvia* L. (Labiatae) species, collected from Antalya, Turkey, were tested for larvicidal activity against the mosquito *Culex pipiens* L. (Diptera: Culicidae) under laboratory conditions. Third and fourth instar mortality from six different concentrations (10, 25, 50, 100, 150 and 200 ppm) of each plant extract were examined. When the results were examined, extract of *Salvia tomentosa* Mill. was the most toxic, followed by those of *S. sclarea* L., *S. argentea* L. and *S. syriaca* L. with LC_{50} values 60.61, 62.05, 107.40 and >200 ppm, respectively. The results indicated that the hexanic extracts of different *Salvia* species may show the high larvicidal activities (Gün, S.Ş. et al. 2011).

In a study conducted in Turkey (2012);

In this study, contact toxicities of methanol extracts of *Humulus lupulus* L., *Bifora radians* Bieb., *Xanthium strumarium* L., *Rhododendron ponticum* L., *Tanacetum mucroniferum* Hub.Mor.& Grierson, *Delphinium consolida* L., *Datura.stramonium* L., *Chrysanthemum segetum* L., *Artemisia vulgaris* L. and *Tanacetum zahlbruckneri* (Nab.) Grierson to *Spodoptera littoralis* (Boisduval) (Lepidoptera: Noctuidae) larvae were tested. *T. zahlbruckneri* appears to be the most toxic plant extract among the tested extracts. In second part of the study, contact toxicity of *T. zahlbruckneri* stem and flower extracts obtained using hexane, ethyl acetate and methanol were tested on *S. littoralis* larvae. The greatest toxicity was recorded with *T. zahlbruckneri* flower-methanol extract by 91% mortality, followed by stem-ethyl acetate (57%) and stem - hexane extracts. Dose-mortality studies with the flower-methanol extract produced 0,013 mg/insect LD_{50} value and 0,039 mg/insect LD_{90} value. These results exhibited that *T. zahlbruckneri extracts*, especially flower-methanol extract, has a potential in the control of cotton leaf worm (Karakoç, C.Ö. & Gökçe, A. 2012).

In a study conducted in Bangladesh (2012);

The insecticidal activity of n-hexane, methanol and water extracts of *Tamarindus indica*, *Azadirachta indica*, *Cucumis sativus*, *Eucalyptus species*, *Switenia mahagoni*, and *Psidium guajava* leaves were investigated by using the Film residue method against a red flour beetle Tribolium castaneum Herbst. The results showed that four plant extracts showed a strong to moderate toxicity at a different concentration on red flour beetle. Among them, *Cucumus sativus* leaves extract showed highest mortality (80%) whereas *Psidium guajava* extract showed lowest mortality (50%). Among the solvents, the hexane extracts showed more toxic effect than other extracts. The LC50 results revealed that the hexane extract of *Cucumus sativus* is the most toxic to the pest followed by the hexane extracts of *Azadirachta indica* and *Tamarindus indica*. Qualitative phytochemical analysis has also been performed (Mostafa, M. et al. 2012).

In a study conducted in Turkey (2016);

Experiments were conducted to investigate the biological effects of essential oils from basil (*Ocimum basilicum* L.), paprika (*Capsicum annuum* L.), peppermint (*Mentha x piperita* L.) and rosemary (*Rosmarinus officinalis* L.) on the different stages of *Ephestia kuehniella* Zeller (Lepidoptera: Pyralidae). Essential oils were obtained by Clevenger-type water distillation and analyzed by capillary gas chromatography-mass spectrometry. The doses of the essential oils applied were 0.1, 1, 5, 10, 20, 50 and 100 µl L^{-1} air. The major compounds of the essential oils were detected as linalool (63.1%), capsaicin (35.4%), menthol (28.3%) and cineole (25.7%), in basil, paprika, peppermint, and rosemary oils, respectively. The essential oil of paprika caused the highest mortality of first instar larvae of *E. kuehniella* at a dose of 5 µl L^{-1} air after 24 h exposure. Among the tested different stages, larvae of *E. kuehniella* were the most tolerant of essential. Basil, paprika, peppermint and rosemary oils exhibited toxicity to adult stages of *E. kuehniella* with 100% mortality obtained after 24 h at dose of 100, 5, 20 and 10 µl L^{-1} air, respectively. Increasing the doses of essential oils resulted in increased toxicity to all stages of *E. kuehniella*. In conclusion, the four plants essential oils tested in this study have potential for use in the management of the stored-product pest, *E. kuehniella* (Pandır, D. & Baş, H. 2016).

In a study conducted in Turkey (2020);

In this study, vapor of essential oil obtained by the hydrodistillation of *Hypericum perforatum* L., 1753 (Malpighiales: Hypericaceae) was tested on the different stages of *Tenebrio molitor* L., 1758 (Coleoptera: Tenebrionidae). The larvae, pupae and adult stages of *T. molitor* were exposed to different doses of *H. perforatum* essential oil for 24 h. After exposure, mortality rate, LC50, LC90 and LC99 values, antioxidant enzyme activities [superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST) and glutathione peroxidase (GPx)], acetylcholinesterase (AChE) activity and malondialdehyde (MDA) levels were measured in the insects. *Tenebrio molitor* was cultured at Gazi University Department of Biology and all analyses were done in Yozgat Bozok University in 2017 and 2018. The results indicated that the pupae of *T. molitor* were the most tolerant and adults were the most sensitive. Mortality increased with the increasing concentration of essential oil. Also, increasing doses of essential oil caused decreasing in SOD, CAT, GST GPx and AChE activities and increasing in MDA level. These results indicate that essential oil of *H. perforatum* can be used against *T. molitor* in a pest control program (Baş, H. & Ersoy, D.E. 2020).

In a study conducted in Tunisia (2008);

Sixteen aromatic plant extracts from three species belonging to the Asteraceae family, were obtained by using organic solvents of increasing polarity. They were tested for insect growth inhibition, contact toxicity and antifeedant activity against adults and lar- vae of confused flour beetle *Tribolium confusum* du Val (Coleoptera Tenebrionidae). Discs made of wheat were incorporated with a single dose of 1% of different extracts. The antifeedant effect, larval growth inhibition and mortality were evaluated in multiple- choice tests. Responses varied with plant-derived material extract, stage of insect and exposure time. Larval growth inhibition was significantly induced by methanolic and ethyl acetate extracts of *Mantisalca duriaei* Briq. et Cavill. and petroleum ether, chloro- formic and methanolic extracts of *Rhaponticum acaule* DC. Antifeedant properties were detected in methanolic extracts of *M. duriaei* and *R. acaule*, petroleum ether and chloroformic extract of *R. acaule* and ethyl acetate extract of *M. duriaei*. *Scorzonera undulata* Vahl seemed to be, however, attractive to the flour beetle. For all extracts, mortality was higher for larvae than adults. It reached respectively 83%, 77% by using petroleum ether and methanol extracts of *R. acaule.* These results suggest that *M. duriaei* and *R. acaule* may be used in grain storage against insect pests (Boussada, O. et al. 2008).

In a study conducted in Canada (2007);

Investigations into the toxicity of three simpler molecules based on the epoxy-alcohol fragment of azadirachtin have revealed insecticidal activity on the greater wax moth *Galleria mellonella* L. larvae. The simpler epoxy-alcohols doses giving 50% mortalities (LD_{50}) for *G. mellonella* larvae were in the increasing order from glycidol (0.022 mg/g), 4,5-epoxy-2-pentanol (0.068 mg/g) and finally, glycerol diglycidyl ether (0.147 mg/g). The three epoxy-alcohols exhibited higher insecticidal activity when compared with the commercial neem product for which the dose giving 50% mortalities was 10.6

mg/g and to azadirachtin that killed the larvae only by injection (dose of 0.20 mg/g of larvae body weight). Our results confirm the importance of the epoxy-alcohol junction between the two parts of the azadirachtin molecule for the biological activity. Other effects of the epoxy-alcohols tested were blackening of larvae and morphological deformities of some adults hatching. In future, the molecules should be complexified (degree of ramification, length of chain and presence of bulky ramified substituent) to obtain an insecticide as toxic for insects only and environmentally safe as azadirachtin but more stable, and their physiological activities on insect's tissues and cells should be studied (Charbonneau, C. et al. 2007).

In a study conducted in Pakistan (2017);

Abstract With the aim of selecting potential botanical insecticides, seven plant extracts (*Daphne mucronata* (Family: Thymelaeaceae), *Tagetes minuta* (Asteraceae), *Calotropis procera* (Apocynaceae), *Boenninghausenia albiflora* (Rutaceae), *Eucalyptus sideroxylon* (Myrtaceae), *Cinnamomum camphora* (Lauraceae) and *Isodon rugosus* (Lamiaceae)) were screened for their toxic effects against four important agricultural pest insects, each representing a separate insect order; pea aphids of *Acyrthosiphon pisum* (Hemiptera), fruit flies of *Drosophila melanogaster* (Diptera), red flour beetles of *Tribolium castaneum* (Coleoptera), and armyworms of *Spodoptera exigua* (Lepidoptera). Aphids were the most susceptible insect with 100% mortality observed after 24 h for all the plant extracts tested. Further bioassays with lower concentrations of the plant extracts against aphids, revealed the extracts from *I. rugosus* (LC_{50} 36 ppm and LC_{90} 102 ppm) and *D. mucronata* (LC_{50} 126 ppm and LC_{90} 198 ppm) to be the most toxic to aphids. These most active plant extracts were further fractionated into different solvent fractions on polarity basis and their insecticidal activity evaluated. While all the fractions showed considerable mortality in aphids, the most active was the butanol fraction from *I. rugosus* with an LC_{50} of 18 ppm and LC_{90} of 48 ppm. Consid- ering that high mortality was observed in aphids within 24 h of exposure to a very low concentration of the butanol fraction from *I. rugosus*, we believe this could be exploited and further developed as a potential plant- based insecticide against sucking insect pests, such as aphids (Khan, S. et al. 2017).

In a study conducted in Turkey (2018);

Origanum, widely used for food and pharmaceutical industries, belonging to the Lamiaceae family, is an aromatic and medicinal plant. The aerial parts of the *Origanum onites* L. were dried at shade and extracted with methanol. Rosmarinic acid, gentisic acid, 4-hydroxybenzoic acid, protocatechuic acid, caffeic acid, vanillic acid, 4-hydroxylbenzaldehyde, *p*-cumaric acid, ferullic acid, apigenin-7-glucoside, and narigenin were found in *O. onites* L. methanol extract. Quantitative analyses of these compounds were determined by LC-TOF/MS and rosmarinic acid was the main constituent (32.05 mg/100 g dried plant). The essential oil was isolated by steam distillation and the isolated compounds were identified by GC-MS analysis. The essential oil included the carvacrol (88.71%) as the main product. *p*-Cymene (3.09%) was found as the second constituting component from frequency point of view. The essential oil exhibited excellent insecticidal activity against *Sitophilus granaries* and *Sitophilus oryzae* pests. However, methanol extract revealed a moderate activity on *S. granarius* pet (Erenler, R. et al. 2018).

In a study conducted in Turkey (2013);

Essential oil vapors obtained by the hydrodistillation of *Prangos ferulacea* (Umbelliferae) were tested on the different stages of *Ephestia kuehniella* Zeller (Lepidoptera: Pyralidae) and egg parasitoid *Trichogramma embryophagum* Hartig (Hymenoptera: Trichogrammatidae). Extracts of the volatile fractions from *P. ferulacea* were analyzed by capillary gas chromatography-mass spectrometry. The major compound of the essential oil was detected as 2,3,6-trimethyl benzaldehyde (66.59%) and the minor compound was heneicosane (0.02%). The third instar larvae of *E. kuehniella* (LC50: 379.662 μL L–1 air and LC99: 538.755 μL L–1 air) and the pupal stage of *T. embryophagum* (LC50: 5.947 μL L–1 air and LC99: 19.568 μL L–1 air) were found to be the most tolerant stages. The essential oil was toxic to the adult stages of both the pest and its parasitoid with 100% mortality obtained after 24 h at 1.0 and 0.25 μL L–1 air, respectively. The LC50 and LC99 values of the essential oil against the egg stages of *E. kuehniella* and *T. embryophagum* were 320.372–486.839 μL L–1 air and 2.121–5.662 μL L–1 air, respectively. In general, the mortality rate increased with the increasing concentration of essential oil. The results of the study indicated that essential oil of *P. ferulacea* should be used as a control agent against *E. kuehniella* for an integrated pest management program (Ercan, F.S. et al.2013).

In a study conducted in Turkey (2018);

In the present study, insecticidal activity of essential oils of *Thymus argaeus* Boissier & Balansa and *Thymus sipyleus* Boissier were evaluated by fumigation method against different developmental stages of *Ephestia kuehniella* Zeller (Lepidoptera: Pyralidae). Essential oils were isolated by Clevenger apparatus. Both essential oils were highly effective against egg and adult stages of pest. On the other hand larvae of *E. kuehniella* were more resistant than other stages. The mortality values reached 100% when the adults were exposed to 5 and 1,5 µl/L air concentrations of *T. argaeus* and *T. sipyleus* essential oil, respectively. In all stages, *T. sipyleus* essential oil was found to be more effective than *T. argaeus* essential oil. Results showed that these essential oils have potential as fumigants against *E. kuehniella* under storage conditions (Ercan, F.S. et al 2018).

In a study conducted in India (1997);

Methanol extracts from 84 samples of 49 Indian plant species in 30 families were tested for insecticidal activities against the brown planthopper *(Nilaparvata lugens* Stâl), using a topical application method. The activity varied with both plant species and tissue sampled. At a dose of 0.5 µg/female, the following 11 extracts indicated significant insecticidal activity: *Adhatoda vasica* leaves (100% mortality), *Annona squamosa* seeds (100%), *Nerıum indicum* stems (100%), *Clerodendrum inerme* whole plants (90%), *Pongamia pinnata* seeds (95%), *Prosopis chinensis* stems (90%), *Vitex negundo* leaves (90%), *Azadirachta indica* seeds (89%) and stems (85%), *Aegle marmelos* leaves (88%), and *Madhuca indica* seed oil (88%). However, the extract of *A. squamosa* seeds alone exhibited significant activity (100% mortality) even at 0.25 µg/female. As naturally occurring insecticides, these tropical plant derived materials could be useful as an alternative for synthetic insecticides in management of field populations of *N. lugens* (Hiremath, I.G. et al 1997).

In a study conducted in Ethiopia (2022);

The use of synthetic insecticides against mosquitoes may lead to resistance development and potential health hazards in humans and the environment. Consequently, a paradigm needs to shift towards the alternative use of botanical insecticides that could strengthen an insecticide resistance management programme. This study aimed to assess the insecticidal efects aqueous, hexane, and methanol crude leaf extracts of *Calpurnia aurea*, *Momordica foetida*, and *Zehneria scabra* on an insectary colony of *Anopheles stephensi* larvae and adults. The lowest LC50 values were observed in aqueous extracts of *M. foetida* followed by *Z. scabra* extract and *C. aurea* leaves at 34.61, 35.85, and 38.69 ppm, respectively, against the larvae. Larval mortality was not observed from the hexane extracts and negative control, while the standard larvicide (temephos) achieved 100% mortality. Further, the adulticidal efcacy was greatest for aqueous extract of *Z. scabra* with LC50=176.20 ppm followed by aqueous extract of *C. aurea* (LC50=297.75 ppm) (Mohammed, M. et al 2022).

In a study conducted in Pakistan (2022);

Plant based insecticides are considered among the most economic and ecofriendly chemicals for the protection of plants and stored grains. The cowpea weevil (*Callosbruchus maculatus*) causes more than 90% damage to sored grains in three to six months. The current study investigates insecticidal potentials of five selected botanicals: *Melia azedarach*, *Nicotiana rustica*, *Azadirachta indica*, *Nicotiana tabacum* and *Thuja orientalis*. They are explored at six different concentrations (0.5, 1.0, 1.5, 2.0, 2.5 and 3.0%) against *C. maculatus* and compared to effects of distilled water which is used as a control. Toxicities of 3% (V/V) extracts of *N. tabacum*, *N. rustica*, *A. indica* and *T. orientalis* against *C. maculatus* were 100%, 86.11%, 80.56% and 72.22%, respectively. Maximum mortality was caused by *N. tabacum* and *N. rustica* (100%), followed by *A. indica* (82%), whereas minimum mortality was observed in *T. orientalis* (64%) at 2.5%. Several phytochemicals, alkaloids, saponins, diterphenes, phytosterol, flavonoids and phenols were identified in *N. tabacum* and *N. rustica*, while few were present in *A. indica*. Phytosterol was present in greatest abundance. Saponins were only detected in aqueous extracts of N. rustica and N. tabacum. Taken together, these results indicate the utility of *N. tabacum*, *N. rustica* and *A. indica* as potential botanicals to control pest beetle and cowpea weevil (Akbar, R. et al. 2022).

In a study conducted in Pakistan and China (2020);

Plant extracts contain many active compounds, which are tremendously fruitful for plant defence against several insect pests. The prime objectives of the present study were to calculate the extraction yield and to evaluate the leaf extracts of *Citrullus colocynthis* (L.), *Cannabis indica* (L.) and *Artemisia argyi* (L.) against *Brevicoryne brassicae* and to conduct biochemical analysis by gas chromatography-mass spectrometry (GC-MS). The results suggested that when using ethanol, *C. colocynthis* produced a high dry yield (12.45%), followed by that of *C. indica* and *A. argyi*, which were 12.37% and 10.95%, respectively. The toxicity results showed that *A. argyi* was toxic to *B. brassicae* with an LC50 of 3.91 mg mL−1, followed by the toxicity of *C. colocynthis* and *C. indica*, exhibiting LC50 values of 6.26 and 10.04 mg mL−1, respectively, which were obtained via a residual assay; with a contact assay, the LC50 values of *C. colocynthis*, *C. indica* and *A. argyi* were 0.22 mg mL−1, 1.96 and 2.87 mg mL−1, respectively. The interaction of plant extracts, concentration and time revealed that the maximum mortality based on a concentration of 20 mg L−1 was 55.50%, the time-based mortality was 55% at 72 h of exposure, and the treatment-based mortality was 44.13% for *A. argyi* via the residual assay. On the other hand, the maximum concentration-based mortality was 74.44% at 20 mg mL−1, the time-based mortality was 66.38% after 72 h of exposure, and 57.30% treatment-based mortality was afforded by *A. argyi* via the contact assay. The biochemical analysis presented ten constituents in both the *A. argyi* and *C. colocynthis* extracts and twenty in that of *C. indica*, corresponding to 99.80%, 99.99% and 97% of the total extracts, respectively. Moreover, the detected caryophylleneonides (sesquiterpenes), α-bisabolol and dronabinol (Δ9-THC) from *C. indica* and erucylamide and octasiloxane hexamethyl from *C. colocynthis* exhibited insecticidal properties, which might be responsible for aphid mortality. However, *A. argyi* was evaluated for the first time against *B. brassicae*. It was concluded that all the plant extracts possessed significant insecticidal properties and could be introduced as botanical insecticides after field evaluations (Maqsuud, A. et al.2020).

The important findings of the above studies are given in the Table 1.

Table 1: The findings of the studies about bioinsecticidal potential of plants

Plant	Used Part	Solvent	Pest	Time (day)	Dose	Mortality(%)	References
Acorus calamus L. var. *angustatus* Besser	rhizome	Methanol	*Sitophilus oryzae* L. (adult)	3	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Acorus gramineus Aiton	rhizome	Methanol	*Sitophilus oryzae* L. (adult)	3	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Agastache rugosa (Fisch. & C.A.Mey.) Kuntze	whole plant	Methanol	*Sitophilus oryzae* L. (adult)	3	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Brassica juncea (L.) Czern.	Essential oil	Methanol	*Sitophilus oryzae* L. (adult)	1	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Cinnamomum cassia (L.) D.Don	Essential oil	Methanol	*Sitophilus oryzae* L. (adult)	1	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Cinnamomum sieboldii Meisn.	root bark	Methanol	*Sitophilus oryzae* L. (adult)	2	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Cocholeria armoracia L.	Essential oil	Methanol	*Sitophilus oryzae* L. (adult)	1	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Eugenia caryophyllata	Flower	Methanol	*Sitophilus*	4	3.5	93	S.-I. Kim et

Thunb.	bud		*oryzae* L. (adult)		mg/cm^2		al. 2003.
Foeniculum vulgare Mill.	Fruit	Methanol	*Sitophilus oryzae* L. (adult)	3	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Illicium verum Hook.	fruit	Methanol	*Sitophilus oryzae* L. (adult)	4	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Acorus calamus L. *var. angustatus* Besser	rhizome	Methanol	*Callosobruchus chinensis* L. (adult)	1	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Allium scorodoprasum L.	Essential oil	Methanol	*Callosobruchus chinensis* L. (adult)	2	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Aquilaria agallocha Roxb.	heartwood	Methanol	*Callosobruchus chinensis* L. (adult)	1	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Brassica juncea (L.) Czern.	Essential oil	Methanol	*Callosobruchus chinensis* L. (adult)	1	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Cinnamomum cassia (L.) D.Don	Essential oil	Methanol	*Callosobruchus chinensis* L. (adult)	1	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Cinnamomum sieboldii Meisn.	root bark	Methanol	*Callosobruchus chinensis* L. (adult)	1	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.

Cocholeria armoracia L.	Essential oil	Methanol	*Callosobruchus chinensis* L. (adult)	1	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Eugenia caryophyllata Thunb.	flower bud	Methanol	*Callosobruchus chinensis* L. (adult)	1	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Foeniculum vulgare Mill.	fruit	Methanol	*Callosobruchus chinensis* L. (adult)	2	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Illicium verum Hook.	Fruit	Methanol	*Callosobruchus chinensis* L. (adult)	2	0.7 mg/cm^2	100	S.-I. Kim et al. 2003.
Thymus mandschuricus Ronniger	whole plant	Methanol	*Callosobruchus chinensis* L. (adult)	1	3.5 mg/cm^2	100	S.-I. Kim et al. 2003.
Zanthoxylum piperitum (L.) DC.	Fruit	Methanol	*Callosobruchus chinensis* L. (adult)	2	3.5 mg/cm^2	90	S.-I. Kim et al. 2003.
Zanthoxylum schinifolium Siebold & Zucc.	fruit	Methanol	*Callosobruchus chinensis* L. (adult)	2	3.5 mg/cm^2	80	S.-I. Kim et al. 2003.
Abuta grandifolia (Mart.) Sandwith	whole plant	Dichloromethane	*Aedes aegypti* L. (larvae)	1	2.6 mg/ml	50	Ciccia, G. et al. 2000.
Minthostachys setosa (Briq.) Epling	whole plant	Methanol	*Aedes aegypti* L.	1	25.2 mg/ml	100	Ciccia, G. Et al. 2000.

			(larvae)				
Peganum harmala L.	seed	Methanol	*Tribolium castaneum* Herbst	32	1.38 mg/ml	92	Jbilou, R. et al. 2006.
Salvia tomentosa Mill.	Aerial part	Hexane	*Culex pipiens* L.	3	60.61 ppm	50	Gün, S.Ş. et al. 2011.
Salvia sclarea L.	Aerial part	Hexane	*Culex pipiens* L.	3	62.05 ppm	50	Gün, S.Ş. et al. 2011.
Tanacetum zahlbruckneri (Nab.) Grierson	flower	Methanol	*Spodoptera littoralis* Boisduval (larvae)	1	0,039 mg/ insect	91	Karakoç, C.Ö. & Gökçe, A. 2012.
Cucumis sativus L.	Leaves	n-Hexane	*Tribolium castaneum* Herbst	2	196.48 mg/cm^2	75	Mostafa, M. et al. 2012.
Capsicum annuum L.	Leaves and fruit	Hidrodistilation	*Ephestia kuehniella* Zeller (adult)	1	10 µl/L	100	Pandır, D. & Baş, H. 2016.
Mentha x piperita L.	Leaves	Hidrodistilation	*Ephestia kuehniella* Zeller (adult)	1	5 µl/L	100	Pandır, D. & Baş, H. 2016.
Rosmarinus officinalis L.	Leaves	Hidrodistilation	*Ephestia kuehniella* Zeller (adult)	1	20 µl/L	100	Pandır, D. & Baş, H. 2016.
Capsicum annuum L.	Leaves and fruit	Hidrodistilation-Essential oil	*Ephestia kuehniella*	1	5 µl/L	100	Pandır, D. & Baş, H. 2016.

			Zeller (larvae)				
Hypericum perforatum L.	Aerial parts	Hidrodistilation-Essential oil	*Tenebrio molitor* L. (adult)	1	6.56 µl/L	99	Baş, H. & Ersoy, D.E. 2020.
Hypericum perforatum L.	Aerial parts	Hidrodistilation-Essential oil	*Tenebrio molitor* L. (larvae)	1	18.5 µl/L	99	Baş, H. & Ersoy, D.E. 2020.
Hypericum perforatum L.	Aerial parts	Hidrodistilation-Essential oil	*Tenebrio molitor* L. (pupae)	1	32.0 µl/L	99	Baş, H. & Ersoy, D.E. 2020.
Rhaponticum acaule DC.	Aerial parts	Petroleum ether	*Tribolium confusum* du Val (larvae)	7	5 µl	83	Boussada, O. et al. 2008.
Azadirachta indica A.Juss.	Seeds	Pure oil	*Galleria mellonella* L. (larvae)	7	420/70 mg/g	100	Charbonneau, C. et al. 2007.
Isodon rugosus (Wall.)Codd	Aerial parts	Butanole	*Acyrthosiphon pisum* Harris	1	102 ppm	90	Khan, S. et al. 2017.
Daphne mucronata Royle	Aerial parts	Methanol	*Acyrthosiphon pisum* Harris	1	198 ppm	90	Khan, S. et al. 2017.
Origanum onites L.	Aerial parts	Hydrodistillation-essential oil	*Sitophilus granaries* L.	1	1 µL /insect	99	Erenler, R. et al. 2018.
Origanum onites L.	Aerial parts	Hydrodistillation-essential oil	*Sitophilus oryzae* L.	1	1 µL /insect	97	Erenler, R. et al. 2018.
Origanum onites L.	Aerial parts	Methanol	*Sitophilus granaries* L.	1	1 µL /insect	66	Erenler, R. et al. 2018.

Prangos ferulacea Lindl.	Aerial parts	Hydrodistillation-essential oil	Ephestia kuehniella Zeller (Egg)	1	486.839 µl/L	90	Ercan, F.S. et al.2013.
Prangos ferulacea Lindl.	Aerial parts	Hydrodistillation-essential oil	*Ephestia kuehniella* Zeller (Larvae)	1	538.755 µl/L	90	Ercan, F.S. et al.2013.
Prangos ferulacea Lindl.	Aerial parts	Hydrodistillation-essential oil	*Ephestia kuehniella* Zeller (Adult)	1	1.099 µl/L	90	Ercan, F.S. et al.2013.
Prangos ferulacea Lindl.	Aerial parts	Hydrodistillation-essential oil	*Trichogramma embryophagum* Hartig (Egg)	1	5.662 µl/L	90	Ercan, F.S. et al.2013.
Prangos ferulacea Lindl.	Aerial parts	Hydrodistillation-essential oil	*Trichogramma embryophagum* Hartig (Larvae)	1	19.568 µl/L	90	Ercan, F.S. et al.2013.
Prangos ferulacea Lindl.	Aerial parts	Hydrodistillation-essential oil	*Trichogramma embryophagum* Hartig (Adult)	1	0.283 µl/L	90	Ercan, F.S. et al.2013.
Thymus argaeus Boiss. & Balansa	Aerial parts	Hydrodistillation-essential oil	*Ephestia kuehniella* Zeller (Egg)	1	10.525 µl/L	99	Ercan, F.S. et al 2018.
Thymus argaeus Boiss. & Balansa	Aerial parts	Hydrodistillation-essential oil	*Ephestia kuehniella* Zeller (Larvae)	1	346.651 µl/L	99	Ercan, F.S. et al 2018.
Thymus argaeus Boiss. & Balansa	Aerial parts	Hydrodistillation-essential oil	*Ephestia kuehniella*	1	6.491 µl/L	99	Ercan, F.S. et al 2018.

			lugens Stâl		/female		I.G. et al 1996
Azadirachta indica A.Juss.	seeds	Methanol	*Nilaparvata lugens* Stâl	2	0.5 µg /female	89	Hiremath, I.G. et al 1996
Vitex negundo L.	leaves	Methanol	*Nilaparvata lugens* Stâl	2	0.5 µg /female	90	Hiremath, I.G. et al 1996
Calpurnia aurea Benth.	leaves	Hydrodistillation	*Anopheles stephensi* Liston (Larvae)	1	200 ppm	100	Mohammed, M. et al 2022.
Momordica foetida Schumach.	leaves	Hydrodistillation	*Anopheles stephensi* Liston (Larvae)	1	200 ppm	100	Mohammed, M. et al 2022.
Nicotiana tabacum L.	leaves	Hydrodistillation	*Callosbruchus maculatus* Fabricius	3	2.5 % V/V	100	Akbar, R. et al. 2022.
Nicotiana rustica L.	leaves	Hydrodistillation	*Callosbruchus maculatus* Fabricius	3	2.5 % V/V	100	Akbar, R. et al. 2022.
Azadirachta indica A.Juss.	seed	Hydrodistillation	*Callosbruchus maculatus* Fabricius	3	2.5 % V/V	82	Akbar, R. et al. 2022.
Artemisia argyi L.	leaves	Ethanol	*Brevicoryne brassicae* L.	3	20 mg/L	74	Maqsuud, A. et al.2020.

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CHAPTER 8

Curcuma longa – THE GOLDEN SPICE OF HEALTH

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INTRODUCTION

Curcuma longa, commonly known as turmeric, is a vibrant yellow spice derived from the rhizomes of the *Curcuma longa* plant, which belongs to the ginger family, Zingiberaceae. It is native to South Asia and has been a staple in traditional medicine and culinary practices for thousands of years. This remarkable plant, native to the Indian subcontinent, has not only enriched cuisines around the world with its distinctive flavor and vibrant yellow color but has also been a cornerstone of traditional medicine systems. Its rhizomatous roots, which yield the prized spice, contain a wealth of bioactive compounds, the most notable being curcumin. These compounds have been extensively studied for their medicinal properties, leading to a growing body of research highlighting the diverse therapeutic applications of *Curcuma longa*. In addition to its medicinal significance, *Curcuma longa* has played a pivotal role in the global economy, with India being the largest producer and exporter of this invaluable spice

This chapter explores the multifaceted medicinal and economic importance of *Curcuma longa*, delving into its historical and cultural significance, phytochemical composition, therapeutic applications, and its role in the international spice trade. Drawing upon a wealth of scientific literature, historical records, and economic data, this chapter aims to provide a comprehensive overview of *Curcuma longa*, shedding light on its past, present, and future significance in the realms of medicine and economics.

The historical and cultural importance of *Curcuma longa* cannot be overstated. References to turmeric can be traced back to ancient Sanskrit texts, including the Vedas, where it was celebrated for its auspicious qualities and use in various rituals. Over time, it became an integral part of Indian cuisine and traditional medicine systems, such as Ayurveda and Siddha, where it was revered for its therapeutic properties. The vibrant yellow hue of turmeric has also been used as a natural dye, and its use in traditional clothing and religious ceremonies further underscores its cultural significance (Prasad and Aggarwal, 2011).

Curcuma longa owes its medicinal properties to a complex mixture of bioactive compounds. Chief among them is curcumin, a polyphenolic compound with potent antioxidant and anti-inflammatory properties.

Researchers have identified various other compounds, such as turmerones and zingiberene, which contribute to its therapeutic potential. Understanding the phytochemical composition of *Curcuma longa* is essential for elucidating its diverse biological activities (Aggarwal and Sung, 2009).

The medicinal applications of *Curcuma longa* are vast and encompass a wide range of health conditions. From its anti-inflammatory and antioxidant effects to its potential in managing chronic diseases like cancer, diabetes, and neurodegenerative disorders, the therapeutic potential of curcumin has garnered considerable attention from the scientific community. This chapter will explore the current state of research on the medicinal applications of *Curcuma longa* and its role in modern healthcare (Gupta and Aggarwal, 2013).

Beyond its medicinal properties, *Curcuma longa* is a major player in the global spice trade. India, the world's largest producer of turmeric, contributes significantly to the international spice market. Understanding the economic dynamics of *Curcuma longa*, including its cultivation, processing, and export, is essential for appreciating its economic significance and the livelihoods it supports (Bhawan and Authorities, 2009).

1. CHEMICAL COMPOSITION

Curcumin**:** The most well-known compound in turmeric is curcumin, which is responsible for its bright yellow color. Curcumin is a potent antioxidant and has anti-inflammatory properties, making it a subject of extensive scientific research.

Volatile Oils: Turmeric contains volatile oils such as turmerone and ar-turmerone, which contribute to its aroma and potential health benefits.

Other Compounds: *Curcuma longa* also contains beneficial nutrients like iron, manganese, vitamin C, and dietary fiber.

The chemical composition of *Curcuma longa* is rich and diverse, with curcuminoids being the most well-studied group of compounds in this plant. According to a study published in the journal "Phytochemistry," curcuminoids are the major bioactive constituents of turmeric, comprising approximately 1-6% of its rhizome by weight. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the primary curcuminoids found in turmeric, with curcumin being the most abundant and extensively researched. These compounds are responsible for the characteristic yellow color of turmeric and possess a wide range of pharmacological activities, including anti-inflammatory, antioxidant, and anticancer properties.

In addition to curcuminoids, turmeric also contains essential oils, such as turmerones, which contribute to its flavor and aroma. These volatile compounds are known for their anti-inflammatory and antioxidant effects. Moreover, turmeric contains various other bioactive compounds, including polyphenols, terpenoids, and flavonoids, all of which contribute to its overall medicinal properties. The diverse chemical composition of *Curcuma longa* makes it a subject of significant interest in the field of natural product research, with ongoing investigations into its potential health benefits and therapeutic applications (Gupta et al., 2013; Kocaadam and Şanlier, 2017).

2. MEDICINAL COMPOUNDS

Curcumin: The primary bioactive compound in turmeric is curcumin, known for its anti-inflammatory, antioxidant, and therapeutic properties. It forms the basis of many of turmeric's medicinal indications.

Curcuminoids: Turmeric contains several curcuminoids, each contributing to its medicinal effects, including demethoxycurcumin and bisdemethoxycurcumin.

Curcuma longa, commonly known as turmeric, is a well-recognized herb in traditional medicine due to its rich reservoir of bioactive compounds with various medicinal properties. The primary bioactive compound responsible for many of turmeric's therapeutic effects is curcumin. Curcumin has been extensively studied for its anti-inflammatory, antioxidant, and anti-cancer properties (Aggarwal et al., 2013). It has demonstrated the ability to modulate several signaling pathways involved in inflammation and cell proliferation, making it a promising candidate for the treatment and prevention of chronic diseases such as cancer, arthritis, and cardiovascular diseases (Gupta et al., 2013). Additionally, curcumin has shown potential in neuroprotection and cognitive function improvement, making it a subject of interest in research on neurodegenerative disorders like Alzheimer's disease (Aggarwal et al., 2013).

Apart from curcumin, turmeric contains other bioactive compounds such as turmerones, gingerols, and essential oils, which contribute to its diverse medicinal properties (Prasad et al., 2014). These compounds exhibit anti-inflammatory, anti-microbial, and analgesic activities, further enhancing turmeric's therapeutic potential. Additionally, the synergistic interactions among these compounds, known as the "turmeric effect," have been shown to enhance their bioavailability and efficacy in various therapeutic applications (Aggarwal et al., 2013). While curcumin remains the most extensively studied compound in turmeric, ongoing research continues to unveil the therapeutic potential of these lesser-known constituents, offering exciting prospects for the development of novel medicinal interventions.

Curcuma longa, with its abundant medicinal compounds, particularly curcumin, has garnered substantial attention in scientific research for its multifaceted health benefits. The diverse array of bioactive compounds in turmeric, coupled with their synergistic interactions, underpins its potential as a natural remedy for various chronic diseases and health conditions. Continued investigation into the mechanisms of action and clinical applications of these compounds holds promise for the development of new therapeutic interventions in the realm of modern medicine.

3. MEDICINAL INDICATIONS

Anti-Inflammatory and Antioxidant Effects

Curcumin's potent anti-inflammatory capabilities may make it a valuable tool in managing chronic inflammation, which is implicated in various diseases. Some pharmacological actions of curcumin (diferuloyl methane) have been examined in rats, mice and cats. The compound possesses significant anti-inflammatory activity in acute as well as in chronic models of inflammation. It is as potent as phenylbutazone in the carrageenan oedema test but only half as potent in chronic tests (Srimal and Dhawan, 1973).

Curcumin exhibits strong antioxidant effect through freeradical-scavenging activity (Deogade and Ghate, 2015). Even though curcumin shows antioxidant effect, in order to increase its antioxidant capacity, analogues of curcumin are focused on (Dolai et al., 2011).

Pain Relief

Turmeric can help alleviate pain, making it beneficial for conditions such as arthritis, migraines, and menstrual discomfort. *Curcuma longa*, commonly known as turmeric, has garnered considerable attention in the realm of pain relief due to its rich content of bioactive compounds, notably curcumin. Extensive research has demonstrated that curcumin possesses potent anti-inflammatory and analgesic properties, making it a promising natural remedy for managing pain. Studies have shown that curcumin can inhibit various inflammatory mediators, such as cytokines and enzymes like cyclooxygenase (COX) and lipoxygenase (LOX), which play a pivotal role in pain generation and inflammation. By modulating these pathways, curcumin has been found to alleviate pain associated with conditions such as osteoarthritis, rheumatoid arthritis, and even post-operative pain (Chainani-Wu, 2003; Shep et al., 2019).

Furthermore, curcumin's analgesic effects have been attributed to its ability to influence the release of endogenous opioids and interact with neurotransmitter systems involved in pain perception (Lopresti et al., 2015). These findings highlight curcumin's potential as a natural alternative to traditional pain management approaches, with the advantage of minimal side effects. However, it is important to note that the bioavailability of curcumin can be limited, and its effects may vary depending on the formulation and dosage used. Nevertheless, ongoing research into novel delivery methods and formulations aims to maximize the therapeutic potential of curcumin for pain relief, offering promising prospects for individuals seeking alternative pain management strategies.

Curcuma longa, particularly its bioactive compound curcumin, exhibits significant potential for pain relief through its anti-inflammatory and analgesic properties. While more research is needed to optimize its bioavailability and dosage, the existing body of evidence underscores the potential of turmeric as a natural and well-tolerated option for pain management in various clinical contexts. This highlights the importance of exploring turmeric-derived compounds as complementary or alternative treatments for pain relief, especially in cases where traditional approaches may pose risks of adverse effects or long-term dependency (Kocaadam and Şanlier, 2017).

Digestive Health

Turmeric aids digestion by stimulating bile production and reducing symptoms of indigestion, bloating, and gas. *Curcuma longa* has been studied for its potential impact on digestive health, and its bioactive compound curcumin appears to play a significant role in this regard. Turmeric has a long history of use in traditional medicine for gastrointestinal issues, and modern research supports its therapeutic potential. Curcumin's anti-inflammatory and antioxidant properties may help alleviate symptoms of digestive disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Studies have suggested that curcumin can modulate inflammatory pathways in the gut, reducing inflammation and oxidative stress, which are often implicated in the pathogenesis of these conditions (Hewlings and Kalman, 2017; Bundy et al., 2004).

Furthermore, curcumin's potential to alleviate digestive discomfort extends to its role in promoting gastrointestinal motility. Research has shown that curcumin may enhance gastric emptying and intestinal transit, which can be beneficial for individuals experiencing issues related to sluggish digestion (Sharma et al., 2011). This effect may offer relief for individuals with conditions like dyspepsia or functional dyspepsia. While more research is needed to establish optimal dosages and formulations, the existing evidence suggests that *Curcuma longa*, particularly curcumin, has the potential to support digestive health through its anti-inflammatory, antioxidant, and motility-enhancing properties.

Curcuma longa, and specifically its bioactive compound curcumin, shows promise in promoting digestive health by targeting inflammation, oxidative stress, and gastrointestinal motility. While further clinical studies are necessary to fully understand its mechanisms and therapeutic potential, the current body of evidence underscores the potential of turmeric as a natural option for individuals seeking to alleviate digestive discomfort and improve their overall gastrointestinal well-being. This highlights the importance of continued research into turmeric-derived compounds as potential complementary or alternative treatments for digestive disorders (Kocaadam and Şanlier, 2017).

Cardiovascular Health

Curcumin may contribute to heart health by reducing cholesterol levels, improving blood vessel function, and reducing the risk of heart disease. *Curcuma longa*, with its prominent bioactive compound curcumin, has garnered growing attention for its potential positive impact on cardiovascular health. Several studies suggest that curcumin may play a vital role in reducing the risk of heart disease by targeting key risk factors. One significant avenue is its effect on cholesterol levels. Research has shown that curcumin may help lower levels of low-density lipoprotein (LDL) cholesterol, often referred to as "bad" cholesterol, while increasing high-density lipoprotein (HDL) cholesterol, the "good" kind. These favorable changes in lipid profiles contribute to a healthier cardiovascular system (Sahebkar, 2013).

Furthermore, curcumin's influence extends to improving blood vessel function, which is critical in maintaining heart health. It has been found to enhance endothelial function, the inner lining of blood vessels, and reduce inflammation within these vessels. Improved endothelial function leads to better blood flow and decreased risk of plaque buildup, which can ultimately reduce the risk of atherosclerosis and related cardiovascular events. These findings underscore the potential of *Curcuma longa* as a natural and accessible means of promoting heart health, though further research is still needed to fully elucidate the mechanisms and optimal dosages for its cardiovascular benefits.

Antioxidant Protection

Turmeric's antioxidants neutralize harmful free radicals, potentially reducing the risk of cancer and delaying aging processes. Turmeric, scientifically known as *Curcuma longa*, has gained attention for its potent antioxidant properties, particularly attributed to its bioactive compound curcumin. Antioxidants play a crucial role in neutralizing harmful free radicals, which can cause cellular damage and contribute to various health issues, including cancer and aging. Numerous studies have investigated the potential of curcumin as a natural antioxidant in mitigating the risk of cancer and delaying aging processes.

The antioxidant effect of curcumin in cancer prevention is well-documented. Curcumin's ability to scavenge free radicals and reduce oxidative stress has been linked to its anti-carcinogenic properties (Gupta et al., 2013). Oxidative stress can lead to DNA damage and mutations, which are pivotal in the initiation and progression of cancer. Curcumin not only quenches free radicals but also exerts its influence on multiple signaling pathways involved in cancer development and progression, including inflammation and apoptosis (Aggarwal et al., 2013). Its potential in inhibiting the growth of cancer cells and promoting their programmed cell death has generated significant interest in curcumin-based therapies for various types of cancer (Kunnumakkara et al., 2017). Moreover, curcumin's protective effects on normal cells by enhancing their antioxidant defense mechanisms further contribute to its role in cancer prevention.

In addition to its potential in cancer prevention, curcumin's antioxidant properties have implications for delaying aging processes. Cellular oxidative damage is a hallmark of aging, and antioxidants can help counteract this damage. Curcumin has been shown to activate cellular antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, which are involved in the defense against oxidative stress (Ruby et al., 1995). By enhancing the cellular antioxidant defense mechanisms and reducing oxidative stress, curcumin may contribute to the preservation of cellular and tissue integrity, ultimately slowing down the aging process. While more research is needed to fully elucidate the mechanisms and long-term effects, the existing evidence underscores the potential of *Curcuma longa* and curcumin as natural antioxidants in the pursuit of cancer prevention and anti-aging strategies.

The antioxidant effect of *Curcuma longa*, particularly through its bioactive compound curcumin, holds promise in reducing the risk of cancer and delaying aging processes. Curcumin's ability to neutralize harmful free radicals and modulate various cellular pathways involved in cancer and aging highlights its potential as a valuable dietary adjunct. While ongoing research is necessary to validate its clinical efficacy and optimal dosages, the accumulating evidence encourages further exploration of turmeric-derived compounds as potential contributors to cancer prevention and strategies for healthy aging.

Liver Health

It supports liver function, aiding in detoxification and reducing the risk of liver diseases. *Curcuma longa*, has been recognized for its potential to support liver health and aid in detoxification processes. The liver plays a pivotal role in detoxifying the body by metabolizing and eliminating toxins and harmful substances. Curcumin, the primary bioactive compound in turmeric, has been extensively studied for its hepatoprotective properties. Research suggests that curcumin can promote liver health through various mechanisms, making it a promising natural intervention in reducing the risk of liver diseases.

One key way in which curcumin supports liver health is its ability to enhance the antioxidant defense system in the liver. The liver is particularly vulnerable to oxidative stress due to its high metabolic activity. Curcumin acts as a potent antioxidant by scavenging free radicals and reducing oxidative damage to liver cells (Kumar et al., 2008). It also stimulates the production of endogenous antioxidants like glutathione, helping to bolster the liver's capacity to neutralize harmful compounds. Furthermore, curcumin has anti-inflammatory properties that can mitigate liver inflammation, a common precursor to liver diseases (Hewlings and Kalman, 2017). By reducing oxidative stress and inflammation, curcumin supports overall liver function and resilience.

Another critical aspect of curcumin's impact on liver health is its role in promoting the regeneration of liver tissue. Studies have shown that curcumin can stimulate the proliferation of hepatocytes, the primary functional cells of the liverlee. This regeneration potential is particularly important in the context of liver diseases and damage caused by various factors, including alcohol consumption and viral infections. Additionally, curcumin may inhibit fibrosis, a process that can lead to cirrhosis and irreversible liver damage (Friedman, 2008). These regenerative and anti-fibrotic effects underscore curcumin's potential as a hepatoprotective agent, reducing the risk of liver diseases and supporting liver function.

Curcuma longa, with its bioactive compound curcumin, demonstrates promising effects on liver health by enhancing antioxidant defenses, reducing inflammation, and promoting liver tissue regeneration. Its multifaceted approach to liver protection positions it as a valuable natural remedy in reducing the risk of liver diseases and supporting overall liver function. While further clinical research is needed to validate its therapeutic potential and establish optimal dosages, the existing body of evidence underscores the significance of turmeric-derived compounds in promoting liver health and detoxification processes.

Neurological Conditions

Emerging research suggests that curcumin may have a neuroprotective role in conditions like Alzheimer's disease and Parkinson's disease. Emerging research has shed light on the potential neuroprotective effects of *Curcuma longa*, commonly known as turmeric, particularly attributed to its bioactive compound curcumin. Neurological diseases like Alzheimer's disease and Parkinson's disease are characterized by the progressive degeneration of neurons and associated cognitive or motor impairments. Curcumin's multifaceted properties, including its anti-inflammatory, antioxidant, and anti-amyloidogenic effects, have sparked interest in its therapeutic potential for these devastating conditions.

One of the key mechanisms through which curcumin exerts its neuroprotective effects is its anti-inflammatory action. Chronic inflammation in the brain is a hallmark of many neurological disorders. Curcumin has been shown to modulate inflammatory pathways by suppressing the production of pro-inflammatory cytokines and enzymes (Chainani-Wu, 2003). This anti-inflammatory activity can help reduce neuroinflammation, which is often associated with the progression of Alzheimer's and Parkinson's diseases. Furthermore, curcumin's antioxidant properties contribute to its neuroprotective role by scavenging free radicals and reducing oxidative stress, which is implicated in neuronal damage (Gupta et al., 2012).

Curcumin's potential in inhibiting the aggregation of abnormal protein aggregates, such as beta-amyloid plaques in Alzheimer's disease and alpha-synuclein in Parkinson's disease, is another noteworthy aspect of its neuroprotective action (Kunnumakkara et al., 2017). These protein aggregates are known to contribute to neuronal dysfunction and cell death. Curcumin has been found to interfere with the formation and accumulation of these toxic proteins, potentially slowing down the progression of these neurodegenerative diseases. While much of the research has been conducted in preclinical studies and clinical trials are needed to confirm curcumin's efficacy, these findings offer a promising avenue for future therapeutic interventions in neurological diseases.

Curcuma longa, and specifically its bioactive compound curcumin, shows promise in exerting neuroprotective effects in conditions like Alzheimer's disease and Parkinson's disease. Its anti-inflammatory, antioxidant, and anti-amyloidogenic properties make it a compelling candidate for mitigating the underlying mechanisms of neuronal damage and cognitive or motor dysfunction in these devastating neurological disorders. Ongoing research in this field holds the potential to unlock innovative approaches to managing and possibly delaying the progression of such diseases, offering hope to individuals affected by them.

Skin Care

Topical application of turmeric can treat various skin issues, including acne, eczema, and psoriasis. *Curcuma longa*, has gained recognition for its potential in skincare due to its bioactive compound curcumin. Topical application of turmeric has been studied for its efficacy in treating a range of skin issues, including acne, eczema, and psoriasis. The anti-inflammatory, antimicrobial, and antioxidant properties of curcumin contribute to its therapeutic effects on the skin.

One of the primary skin conditions that turmeric has been investigated for is acne. Acne is often characterized by inflammation and the proliferation of Propionibacterium acnes bacteria on the skin. Curcumin's anti-inflammatory properties can help reduce the redness and swelling associated with acne lesions (Vaughn et al., 2016). Furthermore, its antimicrobial activity may inhibit the growth of acne-causing bacteria (Wang et al., 2014). Studies have shown that topical formulations containing curcumin can lead to a reduction in acne severity and improved skin appearance.

Eczema and psoriasis are chronic skin conditions characterized by redness, inflammation, and itching. Curcumin's anti-inflammatory properties are particularly beneficial in managing these conditions by calming skin irritation and reducing itching (Prasad et al., 2014). Moreover, curcumin's antioxidant activity helps protect skin cells from oxidative stress, which is often associated with eczema and psoriasis (Chainani-Wu, 2003). While more research is needed to establish standardized treatment protocols, the existing evidence suggests that topical application of *Curcuma longa* can be a valuable addition to skincare regimens for individuals with these skin conditions.

Curcuma longa, through its bioactive compound curcumin, offers a promising avenue for skincare by addressing various skin issues, including acne, eczema, and psoriasis. Its anti-inflammatory, antimicrobial, and antioxidant properties make it a versatile and natural option for improving skin health. As research in this field continues to expand, it is likely that we will see the development of innovative skincare products that harness the therapeutic potential of turmeric, offering relief and improved skin quality for individuals dealing with these common dermatological conditions.

Respiratory Health

Turmeric's anti-inflammatory properties may provide relief from respiratory conditions like asthma and bronchitis. *Curcuma longa*, has garnered attention for its potential therapeutic benefits in the context of respiratory health, particularly due to its prominent bioactive compound, curcumin. Emerging research suggests that turmeric's anti-inflammatory properties may offer relief from respiratory conditions such as asthma and bronchitis. These conditions are characterized by airway inflammation and constriction, making curcumin's anti-inflammatory effects a subject of interest for respiratory health.

Asthma, a chronic respiratory condition, is characterized by recurrent episodes of bronchoconstriction and airway inflammation. Curcumin's anti-inflammatory properties have been studied for their potential in mitigating asthma symptoms. Research indicates that curcumin may modulate immune responses in the airways, reducing the production of pro-inflammatory cytokines and chemokines (Hewlings and Kalman, 2017). Additionally, curcumin's antioxidant activity can help neutralize reactive oxygen species, which contribute to airway inflammation in asthma (Sohrabi et al., 2019). While more clinical trials are needed to establish the optimal dosages and formulations for asthma management, the existing evidence suggests that curcumin holds promise as a complementary approach to alleviate symptoms and reduce asthma exacerbations.

Bronchitis, both acute and chronic, is another respiratory condition characterized by airway inflammation. Curcumin's anti-inflammatory properties can help alleviate the inflammation associated with bronchitis. Research suggests that curcumin may inhibit the production of pro-inflammatory mediators, such as prostaglandins and leukotrienes, which play a role in bronchial inflammation (Chainani-Wu, 2003). Furthermore, curcumin's mucolytic properties may assist in breaking down mucus in the airways, offering relief from the cough and congestion often experienced in bronchitis (Prasad et al., 2014). While more clinical studies are needed to confirm its efficacy in bronchitis management, curcumin's potential as a natural anti-inflammatory and mucolytic agent is a promising avenue for future respiratory care.

Curcuma longa, particularly its bioactive compound curcumin, holds potential in promoting respiratory health by virtue of its anti-inflammatory and antioxidant properties. Although further research is necessary to establish standardized treatment protocols and dosages, the emerging evidence suggests that turmeric-derived compounds may provide relief and support in managing respiratory conditions like asthma and bronchitis. This underscores the importance of continued exploration into the therapeutic applications of turmeric in the realm of respiratory health.

Mood and Mental Health

Some studies indicate that curcumin may have a positive impact on mood disorders like depression and anxiety. *Curcuma longa*, has attracted attention for its potential positive impact on mood disorders such as depression and anxiety. Emerging research suggests that curcumin, the primary bioactive compound in turmeric, may possess properties that can influence mood and mental health. While further studies are needed to establish definitive therapeutic protocols, the preliminary findings indicate the potential of curcumin as a complementary approach for individuals experiencing mood disorders.

Depression is a complex mental health condition characterized by persistent sadness, lack of interest or pleasure, and various physical and cognitive symptoms. Curcumin's potential antidepressant effects have been attributed to its ability to modulate neuroinflammation and enhance brain-derived neurotrophic factor (BDNF) levels (Kulkarni et al., 2008). BDNF is essential for neuronal growth, survival, and synaptic plasticity, and its deficiency is associated with depression. Curcumin's anti-inflammatory and antioxidant properties may also help reduce oxidative stress and neuroinflammation, which are implicated in the pathophysiology of depression (Lopresti et al., 2015). While clinical trials are ongoing, the existing evidence suggests that curcumin supplementation may be a valuable adjunct to conventional treatments for depression.

Anxiety disorders, characterized by excessive worry and fear, can significantly impact an individual's quality of life. Curcumin's potential anxiolytic (anxiety-reducing) effects have been explored in animal models and initial human trials. It is believed that curcumin's ability to regulate neurotransmitters such as serotonin and dopamine may contribute to its anti-anxiety properties. Additionally, curcumin's influence on the hypothalamic-pituitary-adrenal (HPA) axis, which plays a key role in stress response, may help alleviate anxiety symptoms (Lopresti et al., 2014). While more rigorous research is needed to confirm these effects in clinical settings, curcumin's potential to modulate neurotransmitter systems and stress responses offers a promising avenue for individuals dealing with anxiety disorders.

Curcuma longa, with its bioactive compound curcumin, holds promise as a natural approach to positively impact mood and mental health, particularly in the context of depression and anxiety disorders. The preliminary evidence suggests that curcumin's anti-inflammatory, antioxidant, and neuroprotective properties may contribute to its potential therapeutic benefits. Further research, including well-designed clinical trials, is essential to elucidate the optimal dosages and treatment protocols, but the emerging findings offer hope for individuals seeking complementary strategies to manage mood disorders and improve their mental well-being.

4. ADMINISTRATION AND PRECAUTIONS

Dosage

The appropriate dosage of turmeric or curcumin supplements varies depending on the condition and individual factors. Consultation with a healthcare provider is advisable. The dosage of *Curcuma longa*, particularly in the form of turmeric or curcumin supplements, is a critical consideration and should be tailored to individual factors and the specific health condition being targeted. It is imperative to emphasize that consultation with a healthcare provider is highly advisable before initiating any turmeric or curcumin supplementation regimen. The appropriate dosage can vary widely based on factors such as age, weight, overall health, and the intended therapeutic purpose. For general health and well-being, daily consumption of turmeric as a spice in cooking or in the form of turmeric tea is considered safe and can provide potential health benefits (Hewlings and Kalman, 2017). However, when using curcumin supplements for specific health conditions, the dosage can range from 500 mg to 2000 mg or more per day, depending on the severity of the condition (Chainani-Wu, 2003). It's crucial to follow the guidance of a healthcare professional who can assess individual health status and provide recommendations tailored to the patient's needs.

The variability in dosages is underscored by the diverse therapeutic applications of turmeric and curcumin. While some studies have reported positive outcomes with lower doses, others have employed higher doses to achieve desired effects. Additionally, the bioavailability of curcumin is relatively low when taken orally, and various formulations and delivery methods have been developed to enhance its absorption (Gupta et al., 2013). This further highlights the importance of healthcare provider consultation to determine the most appropriate form and dosage of *Curcuma longa* supplementation based on individual health conditions and goals. In conclusion, *Curcuma longa* holds significant potential as a natural remedy with a wide range of therapeutic applications. However, due to variations in dosage requirements and potential interactions with medications or medical conditions, consulting a healthcare provider is essential to ensure the safe and effective use of turmeric or curcumin supplements in promoting health and managing specific health conditions.

Safety

Turmeric is generally safe when used as a spice in culinary dishes. However, high doses of curcumin supplements may cause gastrointestinal discomfort. It may also interact with certain medications, so caution is necessary.

Turmeric, scientifically known as *Curcuma longa*, is generally considered safe when used in culinary dishes as a spice. It has been a staple in many cuisines for centuries and is a well-tolerated ingredient. However, when consumed in high doses as curcumin supplements, individuals may experience gastrointestinal discomfort, including stomach upset, diarrhea, or nausea (Hewlings and Kalman, 2017). This is primarily due to curcumin's potential to stimulate bile production, which can lead to digestive disturbances in some individuals. To mitigate these side effects, it is advisable to start with lower doses and gradually increase them, as tolerated, under the guidance of a healthcare provider. Additionally, the use of specialized formulations with enhanced bioavailability can help reduce the risk of gastrointestinal discomfort when taking curcumin supplements (Gupta et al., 2013).

Another important consideration is the potential for curcumin to interact with certain medications. Curcumin may inhibit drug-metabolizing enzymes in the liver, which can affect the metabolism and efficacy of some medications (Prasad et al., 2014). For example, curcumin may interact with anticoagulant medications, antiplatelet drugs, and drugs that lower blood sugar levels. Therefore, individuals taking such medications should exercise caution and consult with their healthcare provider before incorporating curcumin supplements into their routine. Overall, while *Curcuma longa* is generally safe when used in culinary applications, individuals considering the use of curcumin supplements should be aware of potential side effects and drug interactions and seek professional guidance to ensure safe and effective usage.

5. VARIOUS USES

Culinary Delight

Curcuma longa, more commonly known as turmeric, is not just a vibrant spice, but a culinary treasure that has been used for centuries to add flavor, color, and a touch of health benefits to a wide array of dishes. This versatile spice, native to South Asia, imparts a warm, earthy flavor with a slightly bitter undertone, making it an indispensable ingredient in a variety of global cuisines. The rich, golden hue of turmeric, attributed to its active compound curcumin, adds an appealing visual element to dishes, making it a favorite among chefs and home cooks alike (Aggarwal et al., 2013).

Turmeric's culinary uses are diverse and encompass a broad spectrum of dishes, from curries, stews, and soups to rice, vegetables, and even beverages. In Indian cuisine, it is a fundamental component of curry blends and is used to marinate and season meats, enhancing both the flavor and the color of the final dish. In Middle Eastern and North African cuisines, turmeric is a key ingredient in spice mixtures like Ras el Hanout, adding depth to dishes like tagines and rice pilafs. Beyond its taste and color, turmeric is celebrated for its potential health benefits, which have spurred its integration into contemporary cooking. As a testament to its culinary delight and versatility, turmeric continues to captivate the taste buds and culinary creativity of chefs and food enthusiasts worldwide.

Tea and Supplements

Turmeric tea is a popular beverage known for its potential health benefits. Curcumin supplements are also available for those seeking a concentrated dose. Turmeric tea has gained popularity not only for its pleasing flavor but also for the potential health benefits associated with *Curcuma longa*. The spice's active compound, curcumin, is known for its anti-inflammatory and antioxidant properties, making turmeric tea a delightful and healthful beverage choice. It has been traditionally consumed in regions like India and Southeast Asia, where it is often referred to as "golden milk" or "haldi doodh." This warm and comforting drink is made by steeping turmeric powder or grated turmeric root in hot water or milk, often combined with spices like black pepper and ginger (Hewlings and Kalman, 2017). This combination enhances the bioavailability of curcumin, allowing for better absorption and potential health benefits.

For those seeking a more concentrated dose of curcumin, supplements are readily available. Curcumin supplements typically contain a standardized amount of curcuminoids, the active compounds in turmeric, which can provide a more consistent and higher dose compared to turmeric powder or tea. These supplements are often used for their potential anti-inflammatory and antioxidant effects, which have been linked to various health benefits (Chainani-Wu, 2003). However, it's essential to consult with a healthcare provider before starting any supplementation regimen, as curcumin supplements may interact with certain medications and should be used with caution in specific medical conditions. Whether enjoyed as a soothing cup of turmeric tea or taken as a supplement, *Curcuma longa* continues to be a valuable ingredient in promoting overall health and well-being.

Traditional Medicine

The utilization of *Curcuma longa*, commonly known as turmeric, transcends geographical boundaries and cultural distinctions, finding a place in a myriad of traditional medicine systems worldwide. In addition to its prominent role in Ayurvedic and traditional Chinese medicine, turmeric has been a cherished botanical in indigenous healing practices across the globe. Traditional medicine systems, such as Native American, South African, and Indonesian traditional medicine, have all harnessed the therapeutic potential of turmeric. For instance, Native American tribes have used turmeric for its potential anti-inflammatory and digestive benefits, while indigenous South African medicine has incorporated it into remedies for various ailments, including infections and gastrointestinal issues. Indonesian traditional medicine often features turmeric both in topical applications for skin conditions and as a dietary supplement for its anti-inflammatory properties. These diverse applications across different traditional healing systems underscore the versatility and adaptability of *Curcuma longa* as a natural remedy (Eteraf-Oskouei and Najafi, 2013).

The incorporation of turmeric into such a wide range of traditional healing practices is a testament to its long-standing reputation as a potent medicinal herb. The global acceptance of turmeric highlights its multifaceted nature and the enduring human quest to harness the plant's health-promoting qualities. As modern research continues to uncover the scientific basis for many of these traditional uses, *Curcuma longa* remains a fascinating subject of study for scholars seeking to bridge the gap between ancient wisdom and contemporary medical knowledge, preserving the rich cultural heritage of traditional medicine systems while exploring new avenues for healthcare (Shahrajabian et al., 2019).

6. CONCLUSION

In conclusion, *Curcuma longa*, commonly known as turmeric, stands out as a remarkable botanical species with significant medicinal and economic importance. As highlighted in the introduction of this book chapter, the chemical composition of *Curcuma longa* is characterized by its diverse array of bioactive compounds, notably curcuminoids, essential oils, polyphenols, terpenoids, and flavonoids. These constituents collectively contribute to its numerous pharmacological properties, including anti-inflammatory, antioxidant, and anticancer activities, making it a subject of extensive research in the field of natural product studies. Additionally, its vibrant yellow hue and distinctive flavor have solidified its position as a crucial spice in the culinary world, further emphasizing its economic significance.

As we delve deeper into this academic book, we will explore not only the chemical constituents of *Curcuma longa* but also its extensive history of traditional medicinal use and its growing economic importance in global markets. The chapter will shed light on the plant's potential applications in healthcare, agriculture, and industry, emphasizing the multifaceted significance of this botanical treasure. Through comprehensive exploration and analysis, we aim to provide valuable insights into how *Curcuma longa* contributes to the intersection of medicine and economics, underscoring its pivotal role in the world of plants with medicinal and economic importance.

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CHAPTER 9

MEDICAL USES AND IMPORTANCE OF LICORICE

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INTRODUCTION

Glycyrrhiza glabra, recognized as licorice, holds a prominent and enduring role in the realm of medicine, dating back to the origins of agriculture. This distinguished member of the Fabaceae family is not only extensively utilized for its medicinal properties but also finds its place as a food source. The name Glycyrrhiza stems from the Greek words "glykos" signifying "sweet" and "rhiza" meaning "root." Its nomenclature extends to various monikers across languages: "licorice," "liquorice," "glycyrrhiza," "sweet wood," and "Liquiritiae radix" in English. In the German tongue, it is recognized as "süssholz" and "lakritzenwurzel," while in French, it assumes the identity of "reglisse" and "bios doux." The Persian designation encompasses "shirin bayan" and "mak," whereas Italian and Spanish tongues refer to it as "liquirizia" and "regaliz" (Hayashi and Sudo, 2009; Herrera, 2009; Çınar, 2012; Kutlu, 2013; Pastorino et al., 2018).

Although native to Mediterranean regions, *Glycyrrhiza glabra* has journeyed far and wide, establishing its presence in various corners of the world, including Turkey, Ukraine, India, China, and Russia. This versatile plant has extended its influence to the realms of both pharmaceutical and food industries, often becoming an integral component in the production of functional foods and dietary supplements (Hayashi and Sudo, 2009; Herrera, 2009; Çınar, 2012; Kutlu, 2013; Pastorino et al., 2018). The historical utilization of licorice root transcends the epochs of Greek and Roman empires, reaching deep into the annals of traditional medicine and folk remedies. It has manifested multifaceted applications, each shaped by the geographical context and historical period (Armanini et al., 2002).

The roots of its usage can be traced back to the ancient civilizations of Assyria, Egypt, China, and India. Theophrastus and Pedanius Dioscorides, venerable figures in the world of herbalism, not only recognized the plant's medicinal attributes but also cataloged its therapeutic effects (Armanini et al., 2002). In the realm of traditional Chinese medicine, licorice has long held the status of a staple remedy for addressing gastrointestinal maladies, coughs, bronchitis, and arthritis. Even in contemporary times, its usage continues unabated, especially in the treatment of gastritis, peptic ulcers, and respiratory ailments. A unique aspect of its application is its role as a tooth cleanser (Armanini et al., 2002).

Glycyrrhiza glabra occupies a significant industrial niche in the production of food additives, particularly sweeteners and flavoring agents (Mukhopadhyay and Panja, 2008). This aromatic and versatile plant finds its way into a diverse array of products, including tobacco, chewing gum, confectioneries, baked goods, ice cream, and soft drinks (Rizzato et al., 2017). Furthermore, root extracts contribute to applications as foaming agents in the realm of beer production and fire extinguishers. Beyond its traditional and medicinal attributes, the fibers from its roots play a role in diverse materials like insulation, wall panels, and boxboards, after the extraction of medicinal and flavoring constituents. The world of cosmetics recognizes *Glycyrrhiza glabra* as an agent for skin depigmentation. Notably, both licorice root extract and glycyrrhizin have secured the approval for use in foods from esteemed authorities, including the United States Food and Drug Administration, the European Council, and the Joint Expert Committee on Food Additives of the United Nations Food and Agriculture Organization and World Health Organization (FAO, 2005).

Glycyrrhiza glabra emerges as a characteristic herbaceous perennial plant, capable of reaching heights of up to one meter. It features pinnate, or feather-like, leaves, their length spanning from 7 to 15 cm. The plant's blossoms exhibit a palette of colors, ranging from purple to a light white-blue hue. The fruit takes the form of an elongated pod, measuring between 2 to 3 cm, and houses a profusion of seeds. Within the *Glycyrrhiza* genus, nestled in the Fabaceae family, approximately 30 species find their place, including *G. glabra, G. uralensis, G. inflata, G. aspera, G. korshinskyi,* and *G. eurycarpa*. This plant, like its Fabaceae peers, has the remarkable capacity to form a symbiotic alliance with bacteria of the *Rhizobium* genus, a partnership that enables the vital process of nitrogen fixation at the root level. While it displays a preference for moist soils, *Glycyrrhiza glabra* has demonstrated adaptability to a range of soil types, including sandy and clayey compositions. The historical saga of its therapeutic use reaches back to ancient Egyptian times (Fiore et al., 2005).

In the world of *Glycyrrhiza glabra*, the roots reign supreme, while the leaves have typically been dismissed as agricultural waste. Yet, contemporary research has unveiled that the leaves harbor a cadre of compounds found in the roots, albeit in more modest quantities (Hayashi and Sudo, 2009; Siracusa et al., 2011; Pastorino et al., 2018).

1. CHEMICAL COMPOSITION AND BIOACTIVE COMPONENTS

In recent times, there has been extensive exploration of the chemical constituents housed within licorice root (Hayashi et al., 2016; Siracusa et al., 2011; Pastorino et al., 2018). From a nutritional vantage point, licorice proves to be a wellspring of diverse elements. It contributes proteins, amino acids, polysaccharides, simple sugars, and a medley of mineral salts encompassing calcium, phosphorus, sodium, potassium, iron, magnesium, silicon, selenium, manganese, zinc, and copper. Additionally, licorice contains pectins, resins, starches, sterols, and gums (Wang et al., 2015). The lineup extends to encompass estrogens, tannins, phytosterols such as sitosterol and stigmasterol, coumarins, and an array of vitamins, including B1, B2, B3, B5, E, and C, alongside glycosides (Wang et al., 2015).

This herbal treasure chest also harbors several distinctive biological constituents, most notably triterpenes, saponins that account for its sweet taste, and flavonoids (Rizzato et al., 2017; Wang et al., 2015). The predominant sweetening factor in licorice is triterpene saponins. Their content exhibits substantial variation contingent on geographical origins, harvesting conditions, and processing techniques, thereby exerting a tangible influence on licorice's therapeutic attributes (Pastorino et al., 2018; Michael and Murray, 2013). At the core of its roots lies the star player, glycyrrhizin, a compound nearly 50 times sweeter than sucrose, rendering it the pivotal active agent (Yu et al., 2015). Approximately 10% of licorice root's dry weight is attributed to glycyrrhizin, an amalgam of glycyrrhizic acid potassium, calcium, and magnesium salts, spanning a range from 2% to 25% (Rizzato et al., 2017). Post oral ingestion, glycyrrhizin undergoes metabolic transformation by intestinal bacteria, culminating in the formation of 18-glycyrrhetic acid 3-o-monoglucuronide and glycyrrhetic acid (Michael and Murray, 2013).

The radiant yellow hue characterizing licorice can be ascribed to its bounteous flavonoid repertoire. The distinguished flavonoids span across various classes, including flavanones, flavones, flavanols, chalcones, isoflavans, isoflavones, and isoflavanones. The foremost constituents are liquiritigenin (4',7-dihydroxyflavanone) and isoliquiritigenin (2',4,4'-trihydroxychalcone) glycosides. Among their ranks are compounds like liquiritin, isoliquiritin, liquiritin apioside, and licuraside (Rizzato et al., 2017).

The journey of exploration has yielded five novel flavonoids from dried roots, including glukoliquiritin apioside, shinflavanone, shinpterocarpin, prenyllicoflavone A, and 1-methoxyfazolin. The leaves, too, have not been exempt from this bounty, with the isolation of pinocembrin and licoflavanone (Fukui et al., 1988). Leading the pack in the realm of identified isoflavones is glabridin, its concentration within the dry root weight varying between 0.08% and 0.35% (Simmler et al., 2013). Beyond these constituents, the roots shelter an array of phenolic compounds, embracing isoprenoid-modified flavonoids, chromenes, coumarins, dihydrostilbenes, coumestans, benzospirophanes, and dihydrophenanthrenes. Furthermore, the roots exude a symphony of volatile components contributing to licorice's characteristic fragrance. This ensemble includes geraniol, pentanol, hexanol, terpinen-4-ol, and α-terpineol. The essential oil, a derivative of *G. glabra*, boasts additional components such as propionic acid, benzoic acid, furfuraldehyde, 2,3-butanediol, furfuryl formate, maltol, 1-methyl-2-formylpyrrole, and trimethylpyrazine (Chouitah et al., 2011; Pastorino et al., 2018; Michael and Murray, 2013).

2. PHARMACOLOGICAL EFFECTS

Licorice root stands as one of the most ancient and globally embraced herbal remedies. The traditional applications of licorice root, rooted in history, persist in contemporary practices. We shall delve into the paramount pharmacological effects attributed to its pertinent compounds below:

***Antioxidant Activity*:** The utilization of *G. glabra* finds a strong rationale in its potent antioxidant activity. Phenolic compounds are the architects of this influence, proving their efficacy in shielding biological systems from oxidative stress and deterring the initiation of skin damage (Haraguchi et al., 1998; Pastorino et al., 2018; Varsha and Sonam 2013). In addition to flavonoids, you will find compounds like glabridin, hispaglabridin A, and 30-hydroxy-4-O-methylglabridin, all boasting antioxidant properties (Singh et al., 2015). Notably, dihydrostilbene derivatives discovered in *G.*

glabra leaves pack a significant antioxidant punch, as reported by Biondi et al. (2003). Furthermore, *G. glabra* houses licochalcones B and D, renowned for their robust radical-scavenging capabilities and prowess in thwarting microsomal lipid peroxidation (Biondi et al., 2003; Sharma et al., 2016). For those grappling with oxidative stress-induced damage, topical applications of licorice extract formulations offer an effective remedy, fostering skin equilibrium through their high antioxidant content (Castangia et al., 2015).

***Estrogenic and Androgenic Effects*:** The impacts of licorice on cortisol, testosterone synthesis, and estrogenic activity have been recognized for centuries (Armanini et al., 2002; Michael and Murray, 2013). It has been documented that isoflavones can influence sexual development and disrupt the estrogenic cycle, thereby affecting the performance of the ovaries, hypothalamus, and pituitary glands (Kim and Park, 2012). The estrogen-like effect produced by the ethanol extract of licorice can be elucidated by its agonistic influence on MCF-7 breast cancer cells, and this outcome is mediated through 18β-glycyrrhetinic acid (Sharma et al., 2012). Glabridin, a common element in herbal treatments for alleviating menopausal symptoms, displays substantial estrogenic activity, yielding outcomes akin to those of 17β-estradiol (Su Wei Poh et al., 2015; Tamir et al., 2001). In premenopausal human bone cells, the response to 17β-estradiol and glabridin (particularly at higher concentrations) surpasses that of postmenopausal cells, while glabrene (particularly at higher concentrations) is more efficacious in postmenopausal cells (Somjen et al., 2004).

Isoliquiritigenin exhibits potent estrogen-like activity, implying that under physiological conditions, this compound can convert into an active flavonoid, liquiritigenin (Hajirahimkhan et al., 2013). Furthermore, isoliquiritigenin and formononetin have demonstrated stimulatory effects on sperm during fertilization and could potentially serve as therapeutic agents for infertility treatments (Tung et al., 2014; Tung et al., 2015). Moreover, Zamansoltani et al. (2009) disclosed that the alcoholic extract of *G. glabra* exerts antiandrogenic effects, conceivably by augmenting testosterone metabolism, down-regulating androgen receptors, or activating estrogen receptors.

***Pseudoaldosteronism Activity*:** The ingestion of substantial quantities of Glycyrrhiza over an extended duration has been extensively documented as a trigger for a condition termed pseudoaldosteronism syndrome. This syndrome is characterized by manifestations such as high blood pressure, reduced levels of potassium in the blood (hypokalemia), retention of sodium and water, diminished activity of the plasma renin, and suppressed levels of aldosterone in urine and serum (Michael and Murray, 2013; Farese et al., 1991; Stormer et al., 1993; Takeda et al., 1979; Armanini et al., 1983). In typical individuals, the quantity of glycyrrhizin required to incite these adverse effects varies from 0.7 to 1.4 grams, which approximately equates to 10 to 14 grams of the unprocessed plant (Stormer et al., 1993).

Although *Glycyrrhiza glabra* does possess mineralocorticoid properties, about four times weaker than aldosterone, and has the capability to bind to aldosterone receptors, its impact is usually ineffectual in subjects who have undergone adrenalectomy or those afflicted by severe adrenocortical insufficiency. Consequently, it can be deduced that its primary influence predominantly arises from glycyrrhetinic acid obstructing the degradation of aldosterone in the liver. There is evidence to demonstrate that glycyrrhizin and glycyrrhetinic acid deter the operation of the enzyme 5-β-reductase, which serves as the pivotal enzyme responsible for deactivating cortisol, aldosterone, and progesterone. These effects can be advantageously employed in the management of Addison's disease, an acute ailment characterized by adrenal insufficiency (Armanini et al., 1983).

***Anti-inflammatory Activity*:** *Glycyrrhiza glabra*'s historical use in addressing inflammatory conditions has been well-documented, with its anti-inflammatory properties dating back to ancient times (Yang et al., 2017). While many of its anti-inflammatory effects have been attributed to its "cortisol-like" characteristics, it's important to note that *Glycyrrhiza glabra* often counters or contradicts the actions of cortisol (Kumagai et al., 1967). This counteraction against cortisol involves several mechanisms, including the activation of tryptophan oxygenase, stimulation of liver glycogen storage, promotion of liver cholesterol synthesis, inhibition of thymic atrophy, and suppression of adrenocorticotropic hormone synthesis and release. Nevertheless, glycyrrhizin does enhance cortisol's ability to inhibit antibody production, stress responses, and inflammation. One of its mineralocorticoid-like effects, *Glycyrrhiza glabra* primarily influences glucocorticoid metabolism by suppressing 5-β-reductase activity, ultimately extending the half-life of cortisol. Additionally, glycyrrhetinic acid can convert cortisol into the more potent cortisone (Van Uu et al., 2002). Glycyrrhiza's primary cortisol-like effect can be attributed to its capacity to inhibit phospholipase A2 (Okimasa et al., 1983). Furthermore, glycyrrhizin has been observed to inhibit cyclic adenosine monophosphate phosphodiesterase, leading to elevated cyclic adenosine monophosphate levels and increased prostaglandin production in rat peritoneal macrophages. Its applications extend to functioning as an antidote against various toxins, including diphtheria, tetanus, and tetrodotoxin, and it effectively inhibits experimentally induced allergic reactions such as the Arthus phenomenon, Schwartzman phenomenon, and Forssman anaphylaxis (Amer et al., 1974; Ohuchi et al., 1981; Suzuki et al., 1984; Michael and Murray, 2013).

Licorice root offers notable advantages, particularly in addressing conditions like sore throat, cough, and bronchial discomfort (Damle, 2014; Fiore et al., 2005). These benefits are closely linked to the presence of glycyrrhizin, a compound that effectively eases upper respiratory congestion and promotes the secretion of mucus in the trachea (Sharma et al., 2016). Additionally, liquiritin apioside, an active component identified in licorice's methanolic extract, exhibits the capacity to inhibit capsaicin, a substance known to induce coughing (Kamei et al, 2003). Its efficacy in alleviating sore throat has been likened to that of carbenoxolone, a derivative of glycyrrhetinic acid characterized by a steroid-like structure, which stimulates the secretion of gastric mucus (Damle, 2014).

***Hepatoprotective Effect*:** Glycyrrhetinic acid has been found to effectively prevent liver damage induced by substances such as carbon tetrachloride and galactosamine. Its mechanism of action involves two critical aspects: first, it hinders non-enzymatic lipid peroxidation, and second, it inhibits the production of free radicals, primarily achieved through the reduction of cytochrome P450 via Nicotinamide Adenine Dinucleotide Phosphate (NADPH) (Kiso et al., 1984). The hepatoprotective properties of glycyrrhizin and 18β-glycyrrhetic acid are well-established, primarily due to their ability to inhibit the formation of free radicals and lipid peroxidation (Huo et al., 2011; Sharma and Agrawal, 2017). These compounds have also been explored for their effects on non-alcoholic fatty liver disease (Hajiaghamohammadi et al., 2012). Research by Rizzato et al. (2017) highlights that glycyrrhizin and glycyrrhetic acids can help prevent liver damage induced by medications and can positively influence bile acid metabolism in humans. In fact, glycyrrhetic acid is known for its anti-inflammatory and liver-protective properties (Yin et al., 2017), and glycyrrhizin has demonstrated a significant reduction in serum aminotransferases and an improvement in liver histology when compared to a placebo (van Rossum et al., 1998). Moreover, extended use of glycyrrhizin has been reported to prevent the development of hepatocellular carcinoma in individuals with chronic hepatitis C (van Rossum et al., 1998). In vitro studies have shown that glycyrrhizin can modify and suppress the hepatitis B virus surface antigen (Sato et al., 1996).

***Effects on the Cardiovascular System*:** Glycyrrhizin is a prodrug sourced from licorice root, which undergoes conversion into 3β-monoglucuronyl-18β glycyrrhetinic acid (3MGA) and 18β-glycyrrhetinic acid (GA) in the intestines. Both 3MGA and GA have the ability to inhibit the enzyme 11β-hydroxysteroid dehydrogenase type II (11β-HSD2), responsible for converting cortisol to cortisone. The inhibition of this enzyme leads to elevated cortisol levels, attributed to a mild mineralocorticoid excess within the kidneys. This excess stimulates mineralocorticoid receptors, resulting in an increase in systemic vascular resistance. However, the prolonged inhibition of 11-beta-HSD2 due to excessive licorice consumption can have severe, life-threatening consequences. These include hypernatremia (elevated sodium levels), hypokalemia (low potassium levels), and an overall increase in bodily fluid content. This underscores the importance of creating public awareness regarding the potential adverse effects of licorice on cardiovascular health (Deutch et al., 2019).

***Anticancer Effects*:** The constituents found in licorice root possess a diverse array of anti-cancer effects. These properties can be attributed to their ability to induce mitochondrial permeability, thereby triggering apoptosis in tumor cells, particularly through the actions of 18β-glycyrrhetinic and glycyrrhizic acids (Lee et al., 2008; Ohtsuki et al., 1992). Lee et al. (2008) elucidated the detrimental effects of G. glabra on human cervical and uterine tumor cell line SiHa cells. Meanwhile, Ohtsuki et al. (1992) noted that *G. glabra* extracts in water and methanol inhibited Ehrlich ascites tumor cell growth, ultimately reducing the number of cells. The effectiveness of glycyrrhizin and glycyrrhetinic acids in treating gastric cancer has been demonstrated, with glycyrrhizin adept at suppressing thromboxane A2 with low toxicity in lung cancer cells (Deng et al., 2017). Wang et al. (2017) documented the anti-tumor activities of 18β-glycyrrhetinic acid across various cancer types, including breast cancer, ovarian cancer, gastric tumors, and leukemia. It has been found to inhibit the proliferation of HepG2 cells in liver cancer while leaving normal liver cell lines unaffected. Notably, 18β-glycyrrhetinic acid has been observed to enhance the formation of reactive oxygen species, nitric oxide production, and the loss of mitochondrial membrane potential (Hasan et al., 2016). Glycyrrhetinic acid derivatives have displayed promising cytotoxicity against human breast cancer cell lines (MCF-7, MDA-MB-231) (Li et al., 2016). Additionally, their anti-cancer activity against human leukemia has been substantiated through the induction of apoptosis (Huang et al., 2016). Both Kanazawa et al. (2003) and Jung et al. (2006) revealed that isoliquiritigenin effectively inhibits cell growth by arresting the G2/M cell cycle in breast and prostate tumor cells. Furthermore, glabridin has exhibited anti-tumor properties when tested on various human cancer cells (Jiang et al., 2016; Pastorino et al., 2018).

***Antibacterial Activity*:** Alcoholic extracts derived from Glycyrrhiza have demonstrated *in vitro* antimicrobial efficacy against a variety of bacteria and fungi, including *Helicobacter pylori*, *Staphylococcus aureus* (even antibiotic-resistant strains), *Streptococcus mutans*, *Mycobacterium smegmatis, Bacillus subtilis, Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Candida albicans* (Mitscher et al., 1980; Fukai et al., 2002a-2002b; Tsukiyama 2002; Gupta et al., 2008; Wang et al., 2015; Pastorino, et al., 2018). This observed antibacterial activity has been associated with the presence of secondary metabolites, such as saponins, alkaloids, and flavonoids (Fukui et al., 1988; Wang et al. 2015). In particular, compounds isolated from *G. glabra*, including glabridin, glabrol, glabrene, hispaglabridin A, hispaglabridin B, 40-methylglabridin, and 3-hydroxyglabrol, have been identified as responsible for this activity (Wang et al. 2015). The mechanism underlying this activity may involve the suppression of bacterial gene expression, inhibition of bacterial growth, and reduction in bacterial toxin production (Gupta et al., 2008; Wang et al. 2015).

In 2014, Ahn et al. demonstrated that licorice root can prevent bacterial tooth decay caused by *Streptococcus mutans* and *Streptococcus sobrinus*. The inactivation of methicillin-resistant *Staphylococcus aureus* (MRSA) was attributed to its ability to reduce the expression of MRSA's key virulence genes, SaeR and Hla (Fukai et al., 2002a, 2002b; L. Wang et al., 2015). The antibacterial effect of *G. glabra* on *Mycobacterium tuberculosis* was shown, with glabridin identified as the responsible compound (Simmler et al., 2013). The efficacy of *G. glabra* against *Helicobacter pylori* has also been reported, with glabridin and glabrene as the compounds responsible (Krausse et al., 2004). Additionally, Cao et al. (2016) reported that 18β-glycyrrhetinic acid significantly reduced Helicobacter pylori-induced gastritis infection. Glycyrrhiza root's methanolic extract has been reported to exhibit fungicidal activity against *Arthrinium sacchari* and *Chaetomium funicola*, with glabridin identified as the active compound responsible for these effects (Sato et al., 2000).

Antiviral Effects: *Glycyrrhiza glabra* extracts have been documented to display antiviral properties against a range of viruses, including *Herpes simplex*, *Varicella zoster*, influenza, and *Vesicular stomatitis* virus. This antiviral activity has been attributed to two triterpenoids, glycyrrhizin and 18β-glycyrrhetinic acid. These compounds possess the capacity to impede virus gene expression and replication, reduce adhesion strength and stress, and diminish HMGB1 binding to DNA. Furthermore, they can boost host cell functions by stimulating T lymphocyte proliferation and suppressing host cell apoptosis (Wang et al., 2015; Pastorino et al., 2018). Both glycyrrhizin and 18β-glycyrrhetinic acid primarily hinder virus attachment and entry during the early phases of the virus replication cycle. Among the viruses that affect humans and animals, herpes simplex virus (HSV) stands out as one of the most prevalent. During HSV infection, cellular adhesion increases, contributing significantly to the inflammatory response. Glycyrrhizin enhances the immune response of mice against HSV-1 infection (Sekizawa et al., 2001). Moreover, glycyrrhetinic acid exhibits specific effectiveness against Kaposi's sarcoma-associated herpesvirus (KSHV). In situations where all other drugs are ineffective, glycyrrhetinic acid has been proven to terminate latent KSHV infection (Damle, 2014). Glycyrrhizin has also been employed in the treatment of HIV-1-infected patients (Wang et al., 2015). The outcomes have revealed a reduced concentration of P24 antigen in patients, potentially attributable to the upregulation of chemokines (Sabde et al., 2011). Glycyrrhizin has been found to impact cellular signaling pathways, including protein kinase C, casein kinase II, and activator protein 1, as well as nuclear factor κB (Cinatl et al., 2003).

Gastrointestinal Effects: Licorice root has been shown to effectively heal ulcers and exhibit similar efficacy to H2 blockers (Kassir et al., 1985; Aly et al., 2005; Bardhan et al., 1978). Glycyrrhizinic acid, one of the main components of licorice, possesses antiulcer properties by increasing the concentration of prostaglandins in the stomach, which promote mucus secretion and cell proliferation, contributing to the healing of ulcers. This effect has been observed in experimental studies (Van Marle et al., 1981; Baker, 1994).

Anxiolytic, Antidepressant, and Sedative Effects: *Glycyrrhiza glabra* has been demonstrated to function as a modulator of GABA-A receptors, which are targeted by anesthetics, as well as neuroleptic, anxiolytic, and anticonvulsant compounds. GABA (gamma-aminobutyric acid) serves as the principal inhibitory neurotransmitter in the central nervous system, and GABA-A receptors play a pivotal role in mediating its effects. Consequently, *G. glabra* has the potential to induce sedative and anxiolytic effects (Hoffmann et al., 2016). Furthermore, owing to glabridin's ability to penetrate the blood-brain barrier, it may contribute to hypnotic effects (Simmler et al., 2013). Moreover, extracts derived from licorice root exhibit therapeutic promise in the realm of depressive disorders. In a study conducted with mice, it is believed that the extract interacts with α1-adrenoreceptors and dopamine D2 receptors, thereby increasing norepinephrine and dopamine levels in the mice's brains (Dhingra and Sharma, 2006). The antidepressant impact of licorice root extract can be attributed to the restoration of brain monoamines like norepinephrine and dopamine, as evidenced by its reversal of reserpine-induced depression.

Dermal Effects

***Eczema and Psoriasis*:** Glycyrrhetinic acid demonstrates effectiveness in treating eczema, contact and allergic dermatitis, and psoriasis, similar to topical hydrocortisone. Numerous studies have indicated that glycyrrhetinic acid is particularly potent, especially in chronic cases, surpassing the efficacy of topical cortisone. It can also enhance the effects of topical hydrocortisone by inhibiting 11-β-hydroxysteroid dehydrogenase, the enzyme responsible for converting hydrocortisone into its inactive form (Saeedi et al., 2003; Teelucksingh et al., 1990; Sigurjonsdottir et al., 2003).

***Herpes* Simplex**: Clinical research has shown that topical glycyrrhetinic acid and its derivatives are significantly beneficial in reducing the healing time and alleviating pain associated with cold sores and genital herpes. Glycyrrhizin renders HSV-1 (Herpes Simplex Virus 1) irreversibly ineffective and stimulates the synthesis and release of interferons (Partridge and Poswillo, 1984; Csonka and Tyrrell, 1984).

Melasma*:** Glabrene and isoliquiritigenin have the capacity to inhibit tyrosinase, a vital enzyme involved in melanin synthesis. Conditions like melasma, age spots, and areas affected by actinic damage are a result of melanin accumulation. Glabrene and isoliquiritigenin are potential candidates for use in skin lightening agents (Nerya et al., 2003).***

3. CLINICAL APPLICATIONS

Licorice root's clinical applications can be categorized into four main groups. These different formulations of licorice root are used in the treatment of various health conditions, each with specific biological effects (Michael and Murray, 2013).

Deglycyrrhizinated Licorice (DGL)

Although glycyrrhetinic acid was the initial medication employed for the management of gastric and duodenal ulcers, most medical practitioners now favor DGL for the treatment of peptic ulcers. DGL has proven to be more efficient than glycyrrhetinic acid while causing minimal side effects. Instead of inhibiting the secretion of stomach acid, DGL stimulates the body's natural defense mechanisms, which prevent ulcer formation and promote the healing of damaged mucous membranes without any significant adverse effects. It enhances blood circulation to damaged mucosa, increases the number of mucus-producing cells that safeguard mucosal linings, raises the quantity of mucus these cells generate, and extends the lifespan of intestinal cells. Furthermore, several flavonoid components within *G. glabra* have exhibited substantial efficacy against *H. pylori*, including strains that are resistant to antibiotics (Doll et al., 1962; Wilson, 1972; Van Marle et al., 1981; Fukai et al., 2002).

Oral Licorice Preparations Containing Glycyrrhizin

Oral licorice preparations containing glycyrrhizin are primarily used for the management of the common cold. Furthermore, licorice root components have demonstrated antibacterial properties against prevalent pathogens such as *S. pyogenes*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Another prevalent application of licorice root is in the realm of addressing gynecological concerns, particularly related to conditions like PMS and menopause. In the context of PMS, glycyrrhizin and glycyrrhetinic acid exhibit antiestrogenic effects. By inhibiting the breakdown of progesterone, the utilization of licorice root in the two weeks leading up to the menstrual period (during the mid-luteal phase) can contribute to alleviating PMS symptoms. Clinical trials have revealed the beneficial effects of herbal combinations that include licorice root in the treatment of dysmenorrhea (menstrual cramps). Additionally, isoflavones derived from *Glycyrrhiza glabra* may display some antidepressant effects in PMS, attributed to their ability to inhibit serotonin reuptake (Tanaka et al., 2001; Tanaka, 2003; Ofir et al., 2003).

Licorice Root Flavonoid Oil

LFO holds potential as a treatment for obesity and weight loss. Typically, it is standardized to contain 30% polyphenols and 3% glabridin. The flavonoids are extracted using ethanol and subsequently dissolved in medium-chain triglyceride oil (which constitutes 70% of LFO). The extracted flavonoids from licorice root are primarily hydrophobic components, and there is a negligible presence of hydrophilic components like glycyrrhizin and glycyrrhetinic acid (LFO contains less than 0.005% glycyrrhizic acid). LFO inhibits the activity of key enzymes involved in fatty acid synthesis, such as acetyl-coenzyme A carboxylase and fatty acid synthase, while boosting the enzymatic activity of acyl-coenzyme A dehydrogenase, the crucial enzyme in the fatty acid oxidation pathway. These effects are believed to be responsible for the reduction of visceral fat in both animal and human studies (Honda et al., 2009; Kamisoyama et al., 2008; Aoki et al., 2007; Tominaga et al., 2009).

Topical Preparations Containing Glycyrrhetinic Acid

Preparations of this kind can be used for conditions like eczema, psoriasis, herpes, and melasma.

4. DOSAGE

Dosage for Licorice

The dosing of licorice primarily revolves around the glycyrrhetinic acid content, with one exception in the context of peptic ulcer treatment. For this purpose, DGL (deglycyrrhizinated licorice) is the preferred option as it yields comparable results to glycyrrhetinic acid while being devoid of side effects. The objective is to attain an elevated glycyrrhetinic acid concentration in the bloodstream without eliciting adverse reactions. In general, the following dosages, administered three times a day, are employed to safely and efficiently elevate glycyrrhetinic acid levels (Michael and Murray, 2013):

Dried Root Powder: 1 to 2 grams

Liquid Extract (1:1): 2 to 4 mL

Solid (Dry Powder) Extract (4:1): 250 to 500 mg

It's important to note that consulting with a healthcare professional before using licorice or its derivatives is essential to determine the most suitable dosage for your specific health condition and individual needs.

Dosage for Deglycyrrhizinated Licorice

To be effective in healing peptic ulcers, it has been observed that DGL needs to mix with saliva. DGL (Deglycyrrhizinated Licorice) can enhance the release of salivary compounds that stimulate the growth and regeneration of stomach and intestinal cells. It's worth noting that the capsule form of DGL has not shown the same effectiveness. The standard dosage for DGL is generally two to four 380 mg chewable tablets taken approximately 20 minutes before meals or 20 minutes before meals. This dosage is a common practice used to support stomach and intestinal health and assist in the healing of peptic ulcers (Michael and Murray, 2013).

5. TOXICOLOGY

The primary risks associated with the utilization of licorice root are linked to the mineralocorticoid-like effects of glycyrrhetinic acid. Regular consumption of licorice root (beyond 6 weeks, at a dose exceeding 3 grams per day) or glycyrrhizin (exceeding 100 mg per day) can result in sodium and water retention, hypertension, and hypokalemia. Individuals with preexisting hypertension may be more susceptible to these effects due to an elevated sensitivity to the inhibition of 11-beta-hydroxysteroid dehydrogenase by glycyrrhetinic acid. Monitoring blood pressure and electrolyte levels and increasing potassium intake through dietary means is advised. The most significant impact on blood pressure is typically observed around two weeks after commencement of use. Considerable interindividual variations in sensitivity to glycyrrhizin exist, primarily stemming from pharmacokinetic discrepancies and variances in the conversion to the more potent glycyrrhetinic acid. While adverse effects are generally uncommon at dosages below 100 mg per day, they become more prevalent at dosages exceeding 400 mg per day. Mitigating the adverse effects of glycyrrhizin can be achieved by adhering to a diet rich in potassium and low in sodium.

Licorice root is best avoided by individuals with a history of hypertension, kidney failure, or those already using digitalis preparations. Preparations containing licorice may lead to reduced serum and salivary testosterone levels in men. Glycyrrhetinic acid may undergo enterohepatic circulation, necessitating several days for complete elimination from the body. The use of this herb during premenstrual syndrome may result in water retention and bloating. Furthermore, licorice is contraindicated during pregnancy. Additionally, it has been observed to have abortifacient effects. (Omar et al., 2012; Isbrucker and Burdock, 2006; Koga, et al., 2013;

Armanini et al., 2003; Strandberg et al., 2001; Michael and Murray, 2013; Al-Snafi, 2018).

6. DRUG INTERACTIONS

Liquorice root and its components should be used with caution as they may potentially interact with certain medications. Here are some drug interactions and precautions:

P450 3A4 Drugs: Liquorice root extract and glabridin can inhibit the P450 3A4 enzyme, which plays a role in the metabolism of many drugs. When using liquorice root, the effects of drugs metabolized by P450 3A4 may be enhanced. These drugs include antifungal medications, some calcium channel blockers, immunosuppressants, and others. If you are taking such medications, it is important to review your use of liquorice root with a healthcare professional.

Digoxin: Consumption of liquorice root can enhance the effects of heart medications like digoxin. Individuals using digoxin should exercise caution when using liquorice root and closely monitor their medication doses.

Diuretics and Antihypertensive Drugs: Liquorice root can lead to sodium and water retention, which may affect blood pressure when used in conjunction with diuretics and antihypertensive medications. Those using these medications should consult with their doctors when using liquorice root and regularly monitor their blood pressure.

Oral Hypoglycemic Drugs and Insulin: Liquorice root can lower blood sugar levels. Individuals using oral hypoglycemic drugs or insulin for diabetes management should closely monitor their blood sugar levels while using liquorice root.

7. CONCLUSION

This botanical species has found extensive application in traditional medicine and the culinary sector, particularly as a natural sweetening agent. Its roots are harnessed for averting and alleviating a spectrum of issues, including microbial/viral infections, cancer, and skin ailments. Flavonoids stand out as the most noteworthy bioactive constituents and are acknowledged as the primary agents behind a multitude of biological functions. Distinct phytochemicals like glycyrrhizin, 18β-glycyrrhetinic acid, glabrin A and B, or isoflavones have been pinpointed and linked to diverse biological properties such as antioxidative, antiviral, antimicrobial, anticancer, anti-inflammatory, and hepatoprotective effects. Impressively, these functions frequently align with the collective wisdom of traditional practices and folk medicine. The associated side effects and toxicity of licorice remain notably low, predominantly centered around issues related to hypertension and fluid retention. Especially, only a limited number of investigations have been conducted to date, apart from a few isolated research.

Consequently, prospective areas for future research may revolve around these potential side effects. An essential focus is necessitated for delving into the biochemical exploration and the inherent composition of licorice root. In-depth research is imperative to delve into the intricacies of distinct components of licorice root and various formulations involving licorice root.

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CHAPTER 10

MAIN AND TRACE ELEMENT "CONTENT AND ENRICHMENT" OF GROWING PLANT SPECIES AROUND ESKİŞEHİR BORON MINES IN THE WESTERN ANATOLIA BASIN OF TÜRKİYE

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INTRODUCTION

Plants feed on the elements dissolved in the soil and deeper groundwater by absorbing them with their roots. Therefore, the soil solution represents the soil and groundwater over a large area covered by the roots. Thus, plants growing in the soils of ore-rich regions contain different concentrations of elements compared to the same plant species growing in other regions. If there is a linear relationship between the concentration of elements in the plant and in the soil, this reflects the level of elements in the environment and is called an indicator plant. Since 1965, indicator plants have been fully utilized in this field and about 90 mineral deposits have been identified in many studies (Erdman and Kokkola, 1984; Köksoy, 1991; Özdemir and Sağıroğlu, 1997). In the literature, there are many studies on the determination of indicator plants of elements such as Ni, Cu, Fe, Mn, Pb, Co, Cr, Zn, Mo, Cd, Ti, U and mostly Au.

According to Brooks et al. (1995), in 1961, indicator plants of boron (*Salsola nitraria*, *Eurotia ceratoides*, *Limonium suffruticosum*) were identified in Russia.

Borate deposits in Western Anatolia are generally composed of pebbles, sandstone, tuff, tuffite, claystone, marl and limestone. It shows a distinct cyclicity due to horizontal and vertical facies changes. The presence of volcanic rocks in all basins reveals that volcanism is necessary for the formation of borate and that the boron mineral is dependent on medium and acidic volcanic rocks (Helvacı, 1984). The sediments in borate deposits were generally deposited in arid or semi-arid climatic conditions, in independent or interconnected basins.

All known boron (B) deposits in our country are located in Western Anatolia; south of the Marmara Sea, within an area of approximately 300 km in the east-west direction and 150 km in the north-south direction. Boron (B), a microelement, is an essential element for plants. Although the main function of boron for plants has not yet been fully elucidated, it is known to be especially important in carbohydrate transport.

In this study, about 10 plant species were identified from Boron mine and its vicinity and these are *Euphorbia macroclada* Boiss., *Cirsium creticum* (Lam.) d'Urv. ssp. *creticum*, *Gypsophila perfoliata* L. var. *perfoliata*, *Anchusa* *leptophylla* Roemer & Schultes ssp. *leptophylla, Alyssum sibiricum* Willd, *Echinops microcephalus* Sm., *Centaurea urvillei* DC. ssp. *urvillei, Iberis taurica* DC., *Centaurea virgata* Lam., *Reseda lutea* L. var. *lutea* (Davis, P.H. (ed.) (1965-1985).

The studies carried out to search for promising areas in the earth's crust and to evaluate the deposit from a geological point of view include the prospecting phase.

Biogeochemical prospecting, one of the mineral exploration methods, is one of these methods. Generally, in this method, different organs of plants (branches, leaves, flowers, etc.) are analyzed to evaluate the elemental components they contain and their potential as mineral deposits (Köksoy, 1991).

If there is a linear relationship between the concentration of elements in plants and soil, these plants reflect the level of elements in the environment and are called indicator plants (Erdman and Kokkola, 1984; Köksoy, 1991; Özdemir and Sağıroğlu, 1997).

In geochemical exploration methods, systematic measurements of major and trace elements contained in rocks, stream sediments, soils, plants, waters and gases are used as a guide to locate mineral deposits in the field. Plants have been successfully used as tools in mineral prospecting (Akıncı, 2003).

In mineral exploration, plants are utilized both in biogeochemistry by determining the differences in the chemical composition of plants and in geobotany by observing the morphological and physiological changes of plants growing on ore deposits.

Successful application of biogeochemical prospecting depends on the existence of a linear relationship between the elemental concentration of the mineralization in the soil and the elemental concentration in the plant. Plants that provide this relationship have the ability to indicate the element level in the soil and these plants are called indicator plants (Köksoy, 1991).

Plants growing on ore deposits contain different concentrations of elements compared to the same type of plants growing in other regions. This difference can be in the form of positive (+) anomaly and negative (-) anomaly.

1. IMPORTANT FACTORS IN THE DETECTıON OF BIOGEOCHEMICAL ANOMALIES

In the field, collect abundantly from the dominant plant species. Specimens of the same species should be of the same height and age. In addition, 10-15 samples of at least one plant species should be taken to obtain reliable results.

Any features of the plant that may affect the elemental content should be noted (roadsides, near factories, etc.).

Suitable specimens should be taken at the appropriate time for systematic identification and pressing. May-July is generally preferred for sampling.

- Appropriate methods should be selected for elemental analysis. Samples should be separated into organs (leaf, stem, root, etc.) and analyzed. The results should be evaluated statistically and this evaluation should be done separately for each organ (Erdman and Kokkola, 1984; Köksoy, 1991; Brooks et al., 1995; Özdemir and Sağıroğlu, 1996).

2. ELEMENTAL CONTENT OF PLANTS

Plants take in various elements from the soil and rocks they grow on with their roots.

These elements, which enter the structures of various organs of the plant such as leaves, branches, flowers, etc., then accumulate in the upper part of the soil with the shedding, breakage and death of the plant organs. Thus, the plants carry the elements from the depths to the top of the soil.

Most of the dry weight of plants is composed of C, O, H. The plant obtains these elements from CO_2 and H_2O.Other more important components are N, K, Ca, Mg, P, S and F, respectively.

Although there are many elements in the soil, generally 16 of them are necessary for the growth and development of plants. These elements are called "plant nutrients", "plant nutrients" or simply "plant nutrients" and are divided into macro elements and micro elements. Macro elements are the elements that are needed in large amounts by the plant and are present in excess in the plant (Table 1). These elements are N, P, S, K, Ca, Mg. Micro-elements are the elements that are less abundant in the plant and less taken up by the plant. These elements are Fe, Zn, Mn, Cu, B (Yılmaz, 2004).

Table 1: Elements used as essential nutrients for plants (Yılmaz 2004).

The main elements of organic matter	Macro elements	Micro elements	Elements required only for some plants
C	N	Fe	Al
H	P	Zn	Co
O	S	Mn	Na
	K	Cu	Ni
	Ca	B	Si
	Mg	Cl	V
		Mo	

3. MATERIAL AND METHOD

The plants analyzed in the study were taken from Eskisehir Boron deposits in the Western Anatolia basin of Turkiye.

Elemental contents of the plants were determined by XRF. For this purpose, after the plants were collected, the plants were washed and dried at 80ºC overnight. Then the dried plants were pulverized by crushing in a quartz mortar.

The powdered plants were mixed with blinding wax and 32 mm thick pellets were prepared and multi-element concentrations were determined by polarized energy dispersive XRF.

The measurements were performed on a Spectro XLAB 2000 PEDXRF spectrophotometer equipped with a spectrometer Spectro XLAB 2000 PEDXRF, 0.5 mm Be edge glass and Rh anode X-ray tube.

The detector of the spectrometer is Mn Ka frozen with liquid N2 and Si (Li) at 5000 cps with a resolution < 150eV. The total analysis time for each additional element was 30 min (Stephens and Calder, 2004).

In this study, about 10 plant species were identified in Eskişehir Boron Mine and its vicinity in the Western Anatolia basin of Turkiye. These plants are *Euphorbia macroclada Boiss* (Figure 1), *Cirsium creticum (Lam.) d'Urv.* ssp. *Creticum (*Figure 2), *Gypsophila perfoliata L.* var. *Perfoliata* (Figure 3), *Anchusa leptophylla Roemer & Schultes* ssp. *Leptophylla* (Figure 4), *Alyssum* *sibiricum* Willd. (Figure 5), *Echinops microcephalus* Sm. (Figure 6), *Centaurea urvillei* DC. ssp. *Urvillei* (Figure 7), *Iberis taurica* DC. (Figure 8) *Centaurea virgata* Lam. (Figure 9), *Reseda lutea* L. var. *lutea* (Figure 10) (Photographed by Esra Ergin)

Figure 1: *Euphorbia macroclada* Boiss. growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

Figure 2: *Cirsium creticum* (Lam.) d'Urv. ssp. *creticum* growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

Figure 3: *Gypsophila perfoliata* L. var. *perfoliata* growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

Figure 4: *Anchusa leptophylla* Roemer & Schultes ssp. *leptophylla* growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

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Figure 5: *Alyssum sibiricum* Willd. growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

Figure 6: *Echinops microcephalus* Sm. growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

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Figure 7: *Centaurea urvillei* DC. ssp. *urvillei* growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

Figure 8: *Iberis taurica DC.* growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

Figure 9: *Centaurea virgata* Lam. growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

Figure 10: *Reseda lutea* L. var. *lutea* growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye. (Photographed by Esra Ergin)

4. DISCUSSION

In the analysis using XRF technique, 9 main elements and 38 trace elements were analyzed. However, only 32 elements (Al, Ca, Cr, Fe, K, Mg, Mn, Na, P, S, Si, V, As, Ba, Bi, Cd, Co, Cu, Mo, Ni, Pb, Rb, Sb, Se, Sn, Sr, Th, Tl, U, Zn, Zr, Y) were evaluated as common elements because they were compared with the average elemental analysis of plants in areas with high boron content in the world (Table 1).

According to the analysis results obtained by XRF method, the enrichment factors of the elements were calculated using the following formula (Table 2).

Enrichment Factor;

(EF): [(Element/Al)sample]/ [(Element/Al)standard average]

(Brumsack, 2006).

The averages of the elemental contents of plants from other areas with high boron content in the world were compared with the elemental averages of the plant species identified around the Eskişehir Boron deposit in the Western Anatolia basin of Türkiye. Cr, Mg, Na, S, Si, V, As, Bi, Cd, Co, Mo, Rb, Sb, Sn, Sr, Th, Tl, U, Zr and Y elements are enriched. Ca, Fe, K, Mn, P, Ba, Cu, Ni, Ni, Pb, Se and Zn were depleted (Figure 11 a-k).

The elements enriched and consumed in each plant are as follows in order of abundance.

In *Euphorbia*, the elements Mn < Pb < Se < P < Zn < K < S < Ba < Cu < Mg < Fe < Ni < Ca are depleted and As < Co < Si < Na < V < Cd < Cr < Sr < Rb < Y < Sn < Th < Tl < Mo < Zr < U < Sb < Bi are enriched (Figure 11 a).

In *Cirsium creticum*, Mn < Pb < Zn < P < P < Se < Se < Cu < Fe < Ba < Ba < Ni < Ni < Ca < K < K < Mg < S < Co < As < Cd < Si < Cr < V elements are consumed and Y < Th < Sn < Sn < Mo < Tl < Na < Sr < Sb < Zr < Bi < Rb < U elements are enriched (Figure 11. b).

In *Gypsophila*, Mn < Pb < Zn < Se < Cu < P < Ni < Ba < Fe < K < Ca elements are consumed, and As < Co < Cd < S < Mg < Si < Cr < Na < Sn < Y < Th < V < Tl < Sr < Mo < Sb < Rb < Zr < Bi < U elements are enriched (Figure 11 c).

In *Anchusa leptophylla*, Mn < Pb < Se < P < Zn < K < Cu < Ba < Fe < Ni < Ca < S elements are consumed and Mg < As < Co < Cd < Cd < Si < Cr < Na < V < Y < Sn < Th < Sr < Rb < Tl < Mo < Zr < Sb < Bi < U elements are enriched (Figure 11 d).

In *Alyssum sibiricum*, Mn < Pb < Se < Zn < P < Cu < Cu < Ba < Ni < K < Fe < Ca elements are consumed and S < As < Co < Co < Mg < Cd < Cd <

Cd < Si < Cr < Na < Sn < Y < Th < V < Sr < Tl < Rb < Mo < Sb < Zr < Bi < U elements are enriched (Figure 11 e).

In *Echinops*, Mn < Pb < Se < P < Zn < Cu < Ba < K < Ni < Fe < Ca elements are consumed, while S < Mg < As < Co < Cd < Cd < Si < Si < Cr < Na < Y < Sn < V < Th < Sr < Tl < Rb < Mo < Zr < Sb < Bi < U elements are enriched (Figure 11 f).

In *Centaurea urvillei*, Mn < Pb < Se < Zn < P < Cu < Cu < Ba < K < Ni < Fe < Ca elements are consumed and S < As < Co < Mg < Cd < Cd < Si < Cr < Na < Sn < Y < V < Th < Sr < Tl < Rb < Mo < Sb < Zr < Bi < U elements are enriched (Figure 11 g).

In *Iberis taurica*, Mn < Pb < Se < Zn < P < Cu < Cu < Ba < K < Ni < Fe < Ca elements are consumed and S < As < Mg < Co < Cd < Si < Si < Cr < Na < Sn < Y < V < Th < Sr < Sr < Tl < Rb < Mo < Zr < Sb < Bi < U elements are enriched (Figure 11 h).

In *Centaurea virgata*, Mn < Pb < Se < Zn < P < Cu < Cu < Ba < K < Ni < Fe < Ca elements are consumed and S < As < Co < Mg < Cd < Si < Si < Cr < Na < Sn < Y < V < Th < Sr < Tl < Rb < Mo < Zr < Sb < Bi < U elements are enriched (Figure 11 i).

In *Reseda lutea*, Pb < Mn < Ba < Se < Zn < Cu < Ni < Fe < P < K < Ca < Mg elements are consumed, while S < Si < As < Na < Cd < V < Cr < Sr < Y < Th < Mo < Sn < Tl < Zr < Rb < U < Sb < B elements are enriched (Figure 11 j).

All plant Average is depleted in Mn < Pb < Se < Zn < P < Cu < Cu < Ba < K < Ni < Fe < Ca and enriched in S < Mg < Co < As < Cd < Si < Na < Cr < Y < V < Sn < Th < Sr < Tl < Rb < Mo < Zr < Sb < Bi < U (Figure 11 k).

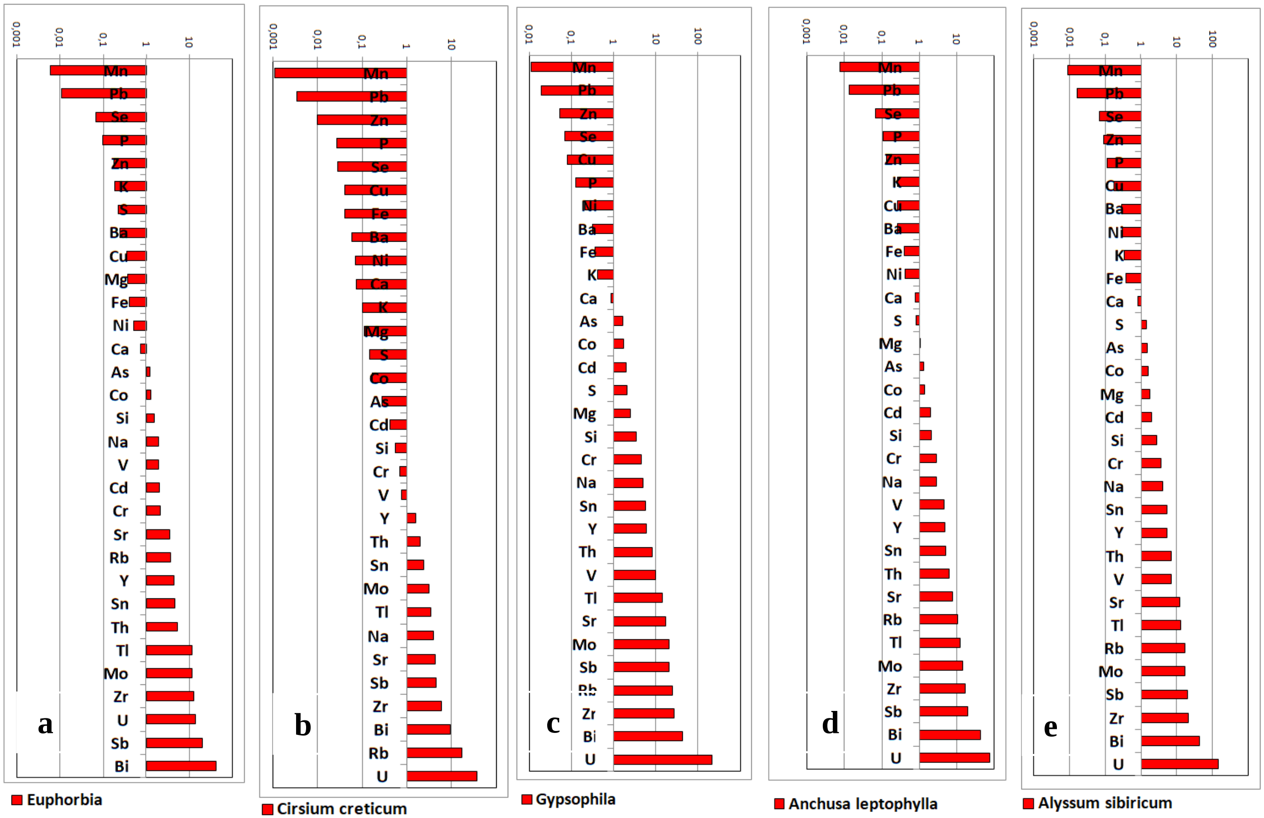
Table 1: Elemental contents of plants growing in the vicinity of Eskişehir Boron Mines in the Western Anatolia basin of Türkiye and averages of elemental contents in plants from other areas with high boron content in the world (ppm)

ElemenT	E . boiss	C. creticum	G. perfoliata	A. leptophylla	A. sibiricum	E. microcephalus	C. urvillei	I. taurica	C. virgata	R. lutea	Analytical Average of all plants in the study area	Elemental Averages of Plants from Areas with High Boron Content in the World (Kabata-Pendias and Pendias 2010)
Al	622,00	622,00	629,00	624,33	626,67	625,50	626,08	625,79	625,94	599,00	622,63	106,00
Ca	22830,00	22830,00	26530,00	24063,33	25296,67	24680,00	24988,33	24834,17	24911,25	21200,00	24216,38	5245,00
Cr	2,40	2,40	5,00	3,27	4,13	3,70	3,92	3,81	3,86	3,70	3,62	0,19
Fe	179,80	179,80	159,60	173,07	166,33	169,70	168,02	168,86	168,44	156,50	169,01	75,00
K	6492,00	6492,00	14380,00	9121,33	11750,67	10436,00	11093,33	10764,67	10929,00	23370,00	11482,90	5975,00
Mg	3142,00	3142,00	20520,00	8934,67	14727,33	11831,00	13279,17	12555,08	12917,13	6270,00	10731,84	1430,00
Mn	21,00	21,00	37,40	26,47	31,93	29,20	30,57	29,88	30,23	23,80	28,15	585,00
Na	290,00	290,00	770,00	450,00	610,00	530,00	570,00	550,00	560,00	330,00	495,00	26,00
P	782,20	782,20	1006,00	856,80	931,40	894,10	912,75	903,43	908,09	3713,00	1169,00	1370,00
S	1710,00	1710,00	15320,00	6246,67	10783,33	8515,00	9649,17	9082,08	9365,63	9437,00	8181,89	1290,00
Si	1798,00	1798,00	3901,00	2499,00	3200,00	2849,50	3024,75	2937,13	2980,94	1817,00	2680,53	196,00
V	1,70	1,70	8,70	4,03	6,37	5,20	5,78	5,49	5,64	2,40	4,70	0,15
As	0,30	0,30	0,40	0,33	0,37	0,35	0,36	0,35	0,36	0,50	0,36	0,04
Ba	42,20	42,20	52,50	45,63	49,07	47,35	48,21	47,78	47,99	8,50	43,14	29,00
Bi	0,50	0,50	0,50	0,50	0,50	0,50	0,50	0,50	0,50	0,40	0,49	0,00
Cd	0,90	0,90	0,90	0,90	0,90	0,90	0,90	0,90	0,90	1,00	0,91	0,08
Co	1,30	1,30	1,70	1,43	1,57	1,50	1,53	1,52	1,53	1,00	1,44	0,17
Cu	10,60	10,60	2,30	7,83	5,07	6,45	5,76	6,10	5,93	4,20	6,48	4,98
Mo	3,10	3,10	5,50	3,90	4,70	4,30	4,50	4,40	4,45	2,50	4,05	0,05
Ni	6,00	6,00	2,40	4,80	3,60	4,20	3,90	4,05	3,98	3,80	4,27	1,97
Pb	1,00	1,00	1,80	1,27	1,53	1,40	1,47	1,43	1,45	0,50	1,29	15,60
Rb	7,50	7,50	49,70	21,57	35,63	28,60	32,12	30,36	31,24	32,70	27,69	0,35
Sb	1,20	1,20	1,20	1,20	1,20	1,20	1,20	1,20	1,20	1,70	1,25	0,01
Se	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,20	0,49
Sn	0,50	0,50	0,60	0,53	0,57	0,55	0,56	0,55	0,56	1,20	0,61	0,02
Sr	237,40	237,40	1111,00	528,60	819,80	674,20	747,00	710,60	728,80	255,40	605,02	11,30
Th	0,60	0,60	0,90	0,70	0,80	0,75	0,78	0,76	0,77	0,60	0,73	0,02
Tl	0,40	0,40	0,50	0,43	0,47	0,45	0,46	0,45	0,46	0,40	0,44	0,01
U	0,40	0,40	6,00	2,27	4,13	3,20	3,67	3,43	3,55	0,60	2,77	0,00
Zn	32,80	32,80	10,10	25,23	17,67	21,45	19,56	20,50	20,03	14,20	21,43	32,00
Zr	4,00	4,00	8,40	5,47	6,93	6,20	6,57	6,38	6,48	4,60	5,90	0,05
Y	0,60	0,60	0,80	0,67	0,73	0,70	0,72	0,71	0,71	0,60	0,68	0,02

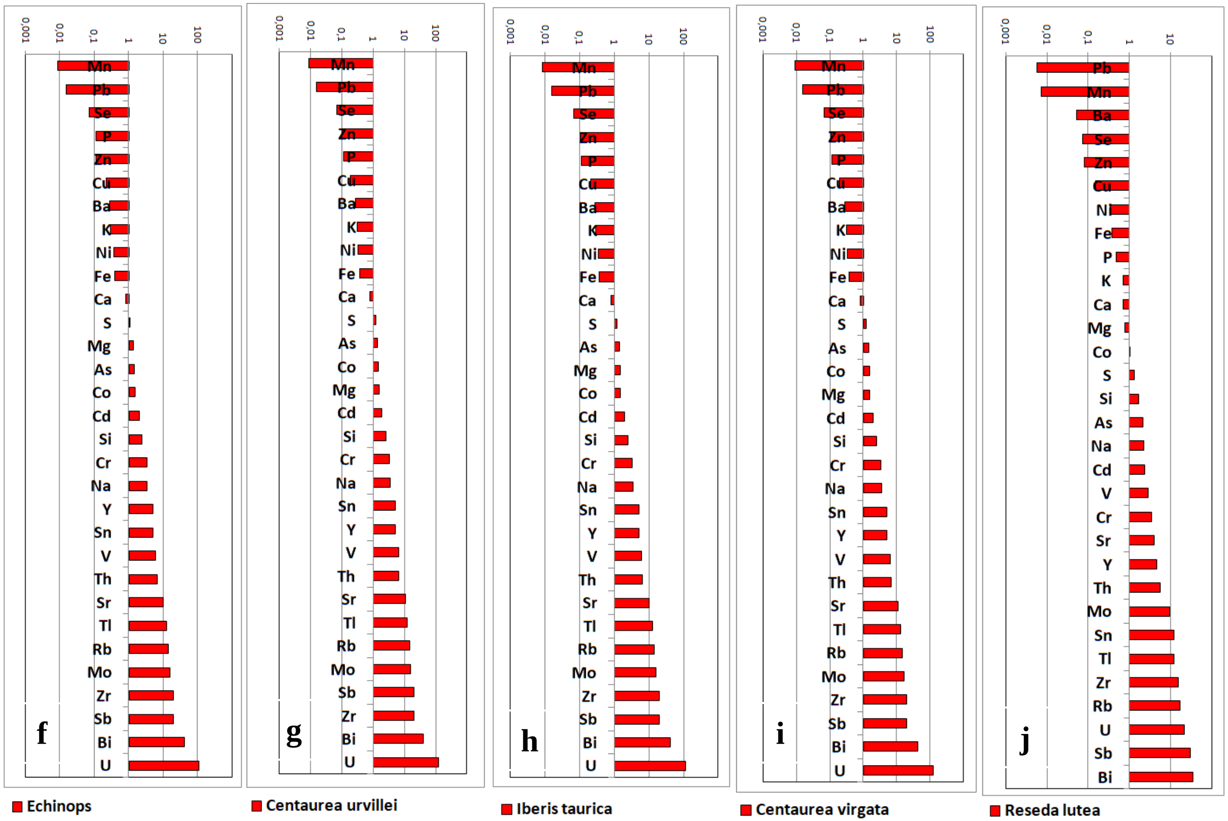
Tablo 2: Element enrichment coefficients of the plant species growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye.

Element enrichment	E . boiss	C. creticum	G. perfoliata	A. leptophylla	A. sibiricum	E. microcephalus	C. urvillei	I. taurica	C. virgata	R. lutea	Analytical Average of all plants in the study are
Ca	0,74	0,07	0,85	0,78	0,82	0,80	0,81	0,80	0,80	0,72	0,79
Cr	2,15	0,70	4,43	2,92	3,68	3,30	3,49	3,40	3,44	3,45	3,24
Fe	0,41	0,04	0,36	0,39	0,38	0,38	0,38	0,38	0,38	0,37	0,38
K	0,19	0,10	0,41	0,26	0,33	0,30	0,31	0,31	0,31	0,69	0,33
Mg	0,37	0,11	2,42	1,06	1,74	1,40	1,57	1,49	1,53	0,78	1,28
Mn	0,01	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
Na	1,90	3,90	4,99	2,94	3,97	3,45	3,71	3,58	3,65	2,25	3,24
P	0,10	0,03	0,12	0,11	0,11	0,11	0,11	0,11	0,11	0,48	0,15
S	0,23	0,14	2,00	0,82	1,41	1,12	1,27	1,19	1,23	1,29	1,08
Si	1,56	0,54	3,35	2,16	2,76	2,46	2,61	2,54	2,58	1,64	2,33
V	1,93	0,74	9,77	4,57	7,18	5,87	6,53	6,20	6,36	2,83	5,34
As	1,22	0,28	1,60	1,35	1,48	1,41	1,44	1,43	1,44	2,11	1,47
Ba	0,25	0,06	0,31	0,27	0,29	0,28	0,28	0,28	0,28	0,05	0,25
Bi	42,60	9,25	42,13	42,45	42,29	42,37	42,33	42,35	42,34	35,39	41,71
Cd	1,99	0,42	1,97	1,98	1,98	1,98	1,98	1,98	1,98	2,30	2,01
Co	1,30	0,17	1,69	1,43	1,56	1,50	1,53	1,51	1,52	1,04	1,44
Cu	0,36	0,04	0,08	0,27	0,17	0,22	0,20	0,21	0,20	0,15	0,22
Mo	11,48	3,07	20,15	14,39	17,28	15,84	16,56	16,20	16,38	9,62	14,97
Ni	0,52	0,07	0,21	0,41	0,31	0,36	0,34	0,35	0,34	0,34	0,37
Pb	0,01	0,00	0,02	0,01	0,02	0,02	0,02	0,02	0,02	0,01	0,01
Rb	3,65	16,72	23,93	10,46	17,22	13,85	15,54	14,69	15,11	16,53	13,47
Sb	20,45	4,37	20,22	20,37	20,30	20,34	20,32	20,33	20,32	30,08	21,28
Se	0,07	0,03	0,07	0,07	0,07	0,07	0,07	0,07	0,07	0,07	0,07
Sn	4,73	2,34	5,62	5,03	5,33	5,18	5,25	5,21	5,23	11,80	5,79
Sr	3,58	4,18	16,57	7,94	12,27	10,11	11,19	10,65	10,92	4,00	9,12
Th	5,38	1,95	7,98	6,26	7,12	6,69	6,91	6,80	6,85	5,59	6,50
Tl	11,36	3,37	14,04	12,26	13,16	12,71	12,93	12,82	12,88	11,80	12,54
U	13,91	37,43	206,35	78,54	142,68	110,67	126,69	118,69	122,69	21,67	96,07
Zn	0,17	0,01	0,05	0,13	0,09	0,11	0,10	0,11	0,11	0,08	0,11
Zr	12,62	6,01	26,21	17,19	21,72	19,46	20,59	20,02	20,31	15,07	18,61
Y	4,45	1,54	5,86	4,92	5,39	5,16	5,28	5,22	5,25	4,62	5,06

*(The results show that values greater than 1 are enriched; values less than 1 are depleted).



a
Mn Pb Se P Zn K S Ba Cu Mg Fe Ni Ca As Co Si Na V Cd Cr Sr Rb Y Sn Th Tl Mo Zr U Sb Bi
Euphorbia
b
Mn Pb Zn P Se Cu Fe Ba Ni Ca K Mg S Co As Cd Si Cr V Y Th Sn Mo Tl Na Sr Sb Zr Bi Rb U
Cirsium creticum
c
Mn Pb Zn Se Cu P Ni Ba Fe K Ca As Co Cd S Mg Si Cr Na Sn Y Th V Tl Sr Mo Sb Rb Zr Bi U
Gypsophila
d
Mn Pb Se P Zn K Cu Ba Fe Ni Ca S Mg As Co Cd Si Cr Na V Y Sn Th Sr Rb Tl Mo Zr Sb Bi U
Anchusa leptophylla
e
Mn Pb Se Zn P Cu Ba Ni K Fe Ca S As Co Mg Cd Si Cr Na Sn Y Th V Sr Tl Rb Mo Sb Zr Bi U
Alyssum sibiricum


f
Echinops
g
Centaurea urvillei
h
Iberis taurica
i
Centaurea virgata
j
Reseda lutea

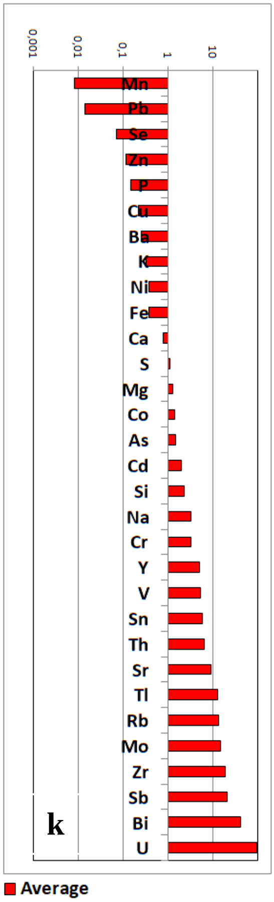


Figure 11 (a-k): Abundance ranking of enriched and consumed elements in plant species growing around Eskişehir Boron Mines in the Western Anatolia basin of Türkiye.

5. CONCLUSIONS

In this study, according to the flora of Turkey, *Euphorbia macroclada* Boiss, *Cirsium creticum* (Lam.) d'Urv. ssp. *creticum*, *Gypsophila perfoliata* L. var. *perfoliata*, *Anchusa leptophylla* Roemer & Schultes ssp. *leptophylla*, *Alyssum sibiricum* Willd., *Echinops microcephalus* Sm., *Centaurea urvillei* DC. ssp. *urvillei*, *Iberis taurica* DC. *Centaurea virgata* Lam., *Reseda lutea* L. var. *lutea* were identified as 10 plant species.

When the elemental analyses on the samples were compared with the world average plant values, it was determined that Cr, Mg, Na, S, Si, V, As, Bi, Cd, Co, Mo, Rb, Sb, Sn, Sr, Th, Tl, U, Zr, Y elements were enriched, while Ca, Fe, K, Mn, P, Ba, Cu, Ni, Pb, Se, Zn were depleted. Among these enriched elements, the enrichment factors of U (~96 times), Bi (~41 times), Sb (~21 times), Zr (~18 times), Mo (~14 times), Rb (~13 times), Tl (~12 times), Sr (~9 times), Th (~6 times), V, Sn and Y (~5 times) are remarkable. These enriched elements are evaluated in order of abundance.

Uranium, which shows the highest enrichment, is an element whose positive biogeochemical response of plants to latent uranium mineralization is well known (Arribas and Herrero-Payo, 1979; Dilabio and Rencz, 1980; Dilabio and Rencz, 1980; Brooks et al. 1982; Dunn, 1981). High concentrations of uranium in the soil can also cause enrichment in the plants growing on it. Plants have an important role in the food chain of all living species. High concentrations of uranium and its decay products in plants can cause harmful effects when they pass through plants to living organisms in the food chain.

Among the heavy metals, bismuth is one of the least abundant elements in the Earth's crust (Kabata-Pendias and Pendias 2010). Generally, bismuth enrichment in soil and living organisms is anthropogenic, such as ferrous and non-ferrous metallurgy, industry and mining (Cabrera et al, 1999). Bismuth, which accumulates in high concentrations in soil, enters the body of plants like other heavy metals (Kabata-Pendias and Pendias 2010, Nagata, 2015). In particular, it concentrates in plant roots. The effects of bismuth on plants and soil are not fully known (Sudina et al 2021).

Volcanic activity and rock weathering is an important source of Sb, but very little Sb is concentrated in the Earth's crust (Baroni et al., 2000). However, human activities such as smelting, mining and fossil burning release large amounts of Sb, resulting in a serious Sb threat in many parts of the world (Tschan et al., 2009). Antimony (Sb) is known as a serious toxic metal and its concentration in soil increases with anthropogenic activities (Ma et al., 2019). Sb is a trace metal used in various industries. It is toxic to all living organisms (Chai et al., 2016). Excessive exposure to Sb can cause cancer, liver and cardiovascular diseases (Herath et al., 2017; Jamali et al., 2017). Due to the oxidizing effects of Sb, it is listed as a top pollutant by the European Union and the US Environmental Protection Agency (Feng et al., 2020, Teng et.al, 2022).

Although most soils contain relatively high amounts of Zr, Zr(OH)5, probably in anionic form, is incorporated into plants. Zirconium content is usually higher in the roots of plants than in their upper parts. Zr has toxic effects on plants and especially on root growth. However, it has also been reported to have positive effects on the growth of some microorganisms and protein synthesis (Ferrand et al. 2006). Zirconium has no known harmful biological role or toxicity and is among the biocompatible elements. Due to this property, it is used in the production of surgical implants and prosthetic devices (Kabata-Pendias and Szteke 2015).

Molybdenum is essential for plants, but the physiological requirement for this element is relatively low. Its availability to plants increases with the pH of the soil. It is directly proportional to its concentration in the soil solution. Molybdenum is moderately mobile in plants. Molybdenum is always more abundant in neutral and alkaline soils. Plants growing in alkaline and neutral soils can concentrate high amounts of Mo (Kabata-Pendias and Szteke 2015).

There is no important mineral dominated by Rb. It is closely related to K minerals. Therefore, it can be found abundantly in pegmatites. It is obtained as a by-product from P, Li and Cs processing and ferrocyanide products. The most important use of Rb is in various chemical and electronic applications. Rb-rich feldspars are used in ceramics. Rb salts are used in biomedical treatments of some patients. Rubidium is readily taken up by plants, similar to other monovalent cations. The available K content controls Rb uptake. The bioavailability of Rb increases in acidic media (pH 3.6-5.0) (Kabata-Pendias and Mukherjee 2007). Rb is toxic if very high concentrations are present in plants. Plants in areas affected by industrial materials always contain higher amounts of Rb (Kabata-Pendias and Szteke 2015).

Thallium content of plants is a function of their concentration in soil. Tl is much higher in grasses and woody plants than in other plant species (Nolan et al. 2004). In plants growing on industrial sites, Tl is easily absorbed and enriched by plants (Adamiec and Helios-Rybicka 2004). Thallium, especially of anthropogenic origin, is easily mobile in soil. Therefore, it is easily translocated into plants through their roots (Al-Najar et al. 2002). Excessive Tl enrichment in plant tissues is considered toxic to all plants.

Sr is not a micronutrient for plants. However, it is absorbed by plants in a similar way to Ca by both mass flux and exchange diffusion mechanisms (ATSDR 2002). The interactions between Sr and Ca are complex. Sr cannot replace Ca in biochemical functions. Increased Ca levels in growth can both inhibit and enhance Sr uptake, depending on the environment and various soil and plant factors. Generally, however, adding Ca to the soil reduces Sr phyto-availability. According to research, the presence of other elements such as Mg, K and Na inhibits Sr uptake from soil to plant (Takeda et al. 2005). Ca-rich boron minerals in the study area may be the source of Sr enrichment.

Thorium is affected by different physico-chemical processes in order to pass from the soil to the plant. Th, which is mobile in the soil, can be easily utilized by plants and usually accumulates in the roots (Shtangeeva 2010). In the phytoremediation technique, hyperaccumulator plants that can absorb heavy metals within the scope of environmental pollutants, accumulate high levels in their tissues and neutralize them after various processes are used. Th-enriched plants are particularly recommended for phytoremediation of contaminated soils (Knox et al. 2008).

Plant transfer of vanadium is influenced by the composition of the soil in which it grows. Vanadium enters the plant much more easily, especially from acidic soils. This indicates that under acidic conditions $VO2+$ is more easily absorbed by the roots. V is also common in neutral and alkaline soils (Selim 2012). Plants in industrial areas can contain very high amounts of V (Kabata-Pendias 2011). There are no studies and no data showing that tin (Sb) is among the essential elements for plants. However, it is assumed to be toxic to plants. Its mobile species, mainly $Sb2+$ and $Sn4+$, are easily utilized by plants and accumulate in the roots. Plants growing in mineralized or contaminated soils are known to have high Sn concentrations (Kabata-Pendias 2011).

Yttrium (Y) is a transition metal in group 3 of the periodic table of elements. It is chemically similar to lanthanides and is usually classified as a rare earth element (REE).

It is never found as a free element in nature. The Y content of higher plants varies depending on soil and climatic factors (Markert and Lieth 1987, Eriksson 2001). Yttrium (mainly as $Y2O3$) is used in luminescent and semiconductor materials applied in various electronic devices, including lasers. It is used in the ceramic and glass industries and in various catalysts (e.g. in the production of plastics). Although yttrium has no known biological effects, exposure to its compounds can cause lung diseases in humans.

The elements enriched in these plant species in the vicinity of Eskişehir Boron mine in the Western Anatolian basin of Türkiye can be used as environmental monitoring tools in biogeochemical prospecting, investigating the environmental impacts of Boron mine and identifying B, Li and Sr contaminated soils.

The soils in the study area where the samples were collected have rich boron content and salinity. High boron (B) content, salinity and toxic element potential of heavy metals organic and inorganic matter can negatively affect living organisms (human, animal, plant) and agricultural soils.

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CHAPTER 11

ECONOMICAL AND MEDICINAL USES OF VARIOUS HEPATOPROTECTIVE HERBAL PLANTS

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INTRODUCTION

Herbal medicine aims at maintaining the homeostatic balance of the body so that body may become able to fight against the certain disease and get cured itself. Each herb or a medicinal plant have one or more active ingredients that decide the suitability of that herb for the treatment of certain diseases. Due to presence of multiple active ingredients in the same plant, it is important to know about the interaction of theses active ingredients with other ingredients and with body of living organisms upon which certain herbal medication is implied.

Liver is the organ of metabolism and hence plays an importany role in the body of an oranism. It helps the conversion of ingested feed/food into enegy, support the blood vascular system and maintain immunity. It also helps the body to get rid of the toxic agents. However, the functioning of liver is some times disturbed due to infections, improper dietary intake. Environmental toxins and other stresses. This disturbance in the physiology leads to pathological condition that include hepatitis, fatty liver and cirrohsis.

Owing to the cetal role of liver in body of organism, when functioning of liver is disturbed then physiology of other related organs will also be affected. Therfore, such medicines are needed to be developed that should have holistic approach to treat multiplr disorders in the body. Keeping in the view, all these facts, this chapter is written to highlight the hepatoprotective significance of *Chelidonium majus*, *Carduus marianus*, *Podophyllum peltatum*, *Aloe vera* L., *Taraxcum officinale*, *Berberis vulgaris* and *Hydrastis canadensis* and their role in the uplift of economy.

1. MEDICINAL USES OF *Chelidonium majus*

C. majus is a perennial herb that grows 30-120 cm (12-47 in) tall. The blue-green leaves are pinnate with lobed and wavy margins and can grow up to 30 cm (12 in) long. On cutting, the plant emits a yellow to orange latex. The blooms have four yellow petals, each about 18 mm (0.71 in) long, and two sepals (Stace et al., 2019). A double-flowered variation occurs naturally.The entire plant is hazardous in relatively small dosage, because it contains a variety of isoquinoline alkaloids. Usage in herbal medicine necessitates the precise dose. Coptisine is the primary alkaloid found in the herb and root. Other alkaloids found in the plant include allocryptopine, stylopine, protopine, norchelidonine, berberine, chelidonine, sanguinarine, chelerythrine, and 8-hydroxydihydrosanguinarine. Sanguinarine is very hazardous, with an LD_{50} of 18 mg per kg body weight. Caffeic acid derivatives, such as caffeoylmalic acid, are also present. Proteolytic enzymes and phytocystatin chelidostatin, a cysteine protease inhibitor, are also found in the distinctive latex (Hahn et. al., 1993). It is an old folk medicine for warts and other skin disorders.

1.1. Effective Liver Tonic

C. majus is the most effective homoeopathic drug for treating liver and gallbladder problems. It is effective in the treatment of various liver problems that include pain, enlarged liver, fatty liver, hepatitis, and jaundice. It helps to manage gall bladder stones and pain due to its impact on the gallbladder. This medication is useful for shooting, stitching, pressing, dull, or throbbing hepatic pain. The pain in the liver spreads to the back and shoulder. Oral intake may alleviate liver pain. The presence of liver complaints accompanied with intense pain under the lower and inner angle of the right scapula. When fatty liver is accompanied by jaundice, *Chelidonium majus* is considered. It is a popular treatment for jaundice. *C. majus* juice is a yellow-like bile that has been used for centuries to treat jaundice. Yellow discoloration of the cheeks, hands, and whites of the eyes occurs in instances where it is required. The stool is black, and the pee smells unpleasant. During the daytime tiredness and poor energy levels are evident. Furthermore, this medication is highly suggested for the relief of gallbladder pain and the dissolution of gallstones (Colombo et al., 1996).

1.2. Effect on Gestro-intestinal Track

The majority of celandine's antispasmodic qualities are ascribed to its alkaloids, which aid digestion, ease cramps, and have anti-inflammatory characteristics. Alkaloids are also thought to be antiviral, antimicrobial, and anti-tumorous. Analgesic, choleretic, immunomodulatory activities have also been identified. Alkaloids are nitrogen-containing chemicals that protect plants against maladies and predators due to their bitter taste. They are also in tomatoes, eggplants, goji berries, and a variety of beverages (Aziz et. al., 2017).

1.3. Effect on Eyes

C. majus was rarely ised to treat eye disorders. It can improve eyeside and treat eye disorders when drops of chalidonium mixed in vodka are put put into eyes. *C. majus* pollen can also be used to treat eyey infections. Furthermore, a popular superstition among inhabitants in the Podolia Region, if some toxin entered into eyes and cause blindness then such blindness could only be cured by *C. majus* (Kujawska et. al., 2017).

1.4. Anti-inflammatory and Immuno-modulatory Impacts

Similar to many other plants, *C. majus* has a number of traditional uses that can be explained by its anti-inflammatory properties that target several physiological pathways as well as immune response regulation. Both have been demonstrated in several studies using cellular models both in vitro and *in vivo*. Controlling inflammation or, in some cases, enhancing immune response and reducing excessive reactivity can improve gastrointestinal symptoms while also having anticancer properties.

In an animal model of ovoalbumine-induced asthma, chelidonine decreased eosinophil-mediated inflammation. The activity was comparable to dexamethasone at 0.5 mg/kg body weight at 1 and 5 mg/kg. Some of the many parameters that were being monitored, including the numbers of various pro-inflammatory cell populations in the bronchoalveolar lavage fluid and lungs, IgE, and the levels of cytokine protein and transcript, were inhibited even more strongly than by dexamethasone (total BALF cells, Gr-1+/CD11b+ cells, IL-4), while others were inhibited in a manner that was comparable. It suggests a specific mechanism involving the transcriptional pathways STAT6 and Foxp3. (Kim et al., 2015). Another disorder, against which *C. majus* is effective, is arthritis (Lee et al., 2015). The previously stated analgesic characteristics of alkaloids can be explained by interactions with glycine transporters (Shin et al., 2003; Jursky and Baliova, 2011). The water extract decreased glycine-activated ion current while increasing glutamate-activated ion current in patch-clamped isolated rat periaqueductal grey (PAG) neurons (Shin et al., 2003).

1.5. Precautions to Use *Chalidonium majus*

Jaundice and mild to severe increases in serum aminotransferase levels are common symptoms of liver damage after using *C. majus* for to 6 months. The inflammation pattern is often hepatocellular, and the clinical presentation and liver histology are similar to that of acute viral hepatitis. Although immunoallergic symptoms are infrequent, autoantibodies may be present at low to moderate levels in many individuals. The clinical condition, on the other hand, seldom mimic autoimmune hepatitis and normally improves quickly after discontinuation of the herb and without the need for corticosteroid treatment (Hoon et. al., 2006).

2. MEDICINAL USES OF *Podophyllum peltatum*

Podophylum peltatum is a member of the Berberidaceae family. It is a perennial herb with an unbranched stem and one to two big, rounded, deeply lobed leaves. The flower is solitary, nodding, between two leaves, and is having six to nine divisions and white. The fruit is apple-like and turns yellow when ripe. The mayapple is the name given to Podophyllum peltatum most frequently, but it is also known as Devil's apple, hog apple, Indian apple, umbrella plant, wild lemon, and American mandrake. Its origins are in the rich forests, fields, and pastures of natural areas in the United States. When poisonous parts like unripe fruit, leaves, or roots are consumed, it causes toxicity. Major signs and symptoms include Depending on how much quantity was consumed, certain symptoms, such as salivation, vomiting, diarrhea, excitement, headaches, fever, and coma, may occur. Fruit that is ripe (yellow and soft) is edible raw but in the limited quamtites (Duke et al., 2002).

2.1. Effective Liver Tonic

Indians originally brought the plant to the attention of European settlers in the New World. In addition to treating digestive problems, the root was used to activate glands. A tonic for stomach, lung, and liver conditions was also made from the root.It helps in maintaining the liver health in animals and as well as in the people. The rheumatism remedy of choice was a decoction made by boiling the roots in water. This was also utilized, to treat poultry with diarrhea. It was once a toxin that was applied to chipmunk eradication.

Intestinal worms are treated with it and laxatives made from the powder are used by people (Foster et al., 1993).

2.2. Antiviral Characteristics

Applying podophyllum resin, also known as podophyllin, topically to the affected area as a 2% to 4% gel or as a 10% to 25% solution in tincture of benzoin will help eradicate warts caused by the human papillomavirus. Podophyllotoxin (podofilox, Condylox), a compound found in podophyllum and a drug approved by the FDA, is often used since it is less toxic and more effective. However, some studies suggest that 20% podophyllum resin is just as effective at treating penile warts as 8% podophyllotoxin or colchicine solutions (Lenfeld et al., 1981).

2.3. Anti Cancerous Properties

Etoposide and teniposide were developed as semi-synthetic epipodophyllotoxin derivatives from Podophyllum peltatum and Podophyllum emodi (Crag et al. 1998). The emetic, cathartic, and anthelmintic properties of podophyllotoxin, which is derived from Podophyllum peltatum, led the Amerindians and early settlers to utilize it as a folk treatment.The most lethal component of the plant is the long, thin rhizome (a horizontal underground stem from which the roots grow), but it is also the most beneficial since it contains high levels of the podophyllotoxin and alpha and beta peltatin, all of which have anticancer characteristics.

In the development of the anticancer drugs, etoposide, and teniposide, as semi synthetic derivatives of epipodophyllotoxins were isolated from Podophyllum peltatum L. and Podophyllum emodiPodophyllotoxin, extracted from Podophyllum peltatum that was was used as a folk remedy by the American Indians and early colonists for its emetic, cathartic and anthelmintic effects.The long, thin rhizome (a horizontal underground stem from which the roots grow) of the plant is the most poisonous part, but also the most useful because it contains high concentrations of the compounds podophyllotoxin and alpha and beta peltatin, all of which have anticancer properties. Etoposide and teniposide, two of the derivatives of podophyllotoxin (podofilox), are all cytostatic (antimitotic) glucosides. Cells going through mitosis are particularly susceptible to the effects of podofilox, an extract from the mayapple. Podophyllotoxin interacts with tubulin at a different place than the vinca alkaloids do. At standard concentrations, etoposide and teniposide have no impact on microtubular structure or function (Chabner et al., 2001).

3. MEDICINAL USES OF *Berberis vulgaris* L.

Asia, Europe, Africa, North America, and South America all have temperate or semitropical climates that are home to the genus *Berberis*. Iran is one of several countries throughout the world where various *Berberis* species are found. *B. vulgaris* fruit are produced on 11,000 hectares of land in Iran each year, making it the world's largest producer of the fruit. Southern Khorasan in Iran is one of the regions where *B. vulgaris* is most widely produced. Over ninety-seven of all *B. vulgaris* production areas and ninety-five percent of all *B. vulgaris* fruit cultivated in Iran are located in Ghaenat County, Southern Khorasan Province. For specialized reasons, different species of the genus Berberis that are found all over the world are cultivated and raised. *B. vulgaris* is the well-known Berberis and is mostly used as a meal when cooked wit rice. *B. vulgaris* is also used for medicine and juice extraction in the food industry (Alemardan et al., 2013).

Numerous studies have documented the pharmacological properties of *B. vulgaris*. In diabetic rats, *B. aristata* root extract reduced blood glucose level and helped to control glucose metabolism (Singh et al., 2009). In addition to *B. vulgaris* tree root extract is useful in both treating and preventing the development of gastrointestinal tract Stones (Bashir et al., 2010). According to (Kosalec et al., 2009), this root extract of the plant has the ability to combat *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*.

3.1. Treatment of Alzheimer's Disease

Berberine is one of the primary components of *B. vulgaris* that can have both curative and protective effects on the central nervous system when taken through route. When administered to diabetic mice, the alkaloid berberine can protect the islets of Langerhans, boost insulin secretion, lower cholesterol and low-density lipoprotein, and increase high-density lipoprotein (Chueh et al., 2014). Salts and other vitamins, such as vitamin C, are present in *B. vulgaris* fruit. Ascorbic acid was found to have a curative impact on dementia development in people with Alzheimer's disease (Chueh et al 2006).

Additionally, it was discovered that ascorbic acid concentration in the plasma had been lowered in dementia patients in comparison to the control group, demonstrating protective role of ascorbic acid in maintaining the neural health (Harrison et al., 2009). Additionally, ascorbic acid has been shown to be effective in enhancing memory in both humans and older animals (Levine et al., 1999). According to various experimental models, ascorbic acid is beneficial at treating memory problems and learning difficulties (Cho et al., 2003).

3.2. Anti diabetic Impact

Aqueous and hydroalcoholic extracts of *B. vulgaris* were administered to mice, and the results showed that *B. vulgaris* affected the islets of Langerhans via a hypoglycemic mechanism. This supported the in vitro antidiabetic effects in low concentrations of blood glucose level. (Ahangarpour et al., 2012). Patients with type 2 diabetes have been demonstrated to benefit from the hypotensive effects of *B. vulgaris* fruit. Additionally, research has demonstrated that using *B. vulgaris* fruit can reduce inflammatory markers in animal models (Golzarandi et al., 2009).

3.3. Hepatoprotective Impacts

In patients, aqueous *B. vulgaris* fruit extract may play a significant effect in reducing cholesterol and triglyceridemia (Farhadi et al., 2008). The preventive effects of *B. vulgaris* extract on liver cytotoxicity brought on by carbon tetrachloride showed that this extract might stop liver damage in mice (Hermenean et al., 2012). The highest inhibitory effect was exerted on glycosilation, and lipid peroxidation was adequately inhibited in the presence of various concentrations of B. vulgaris, according to studies on the antioxidant effect of *B. vulgaris* on oxidative systems such as liver cells oxidation, red blood cells hemolysis, and hemoglobin non-enzymatic glycosylation (Eshraghi et al., 2011). Moderate acne in adolescents was successfully treated with oral administration of an aqueous *B. vulgaris* fruit extract (Fouladi et al., 2012). *E. coli* and *S. aureus* growth were effectively inhibited by a hydroalcoholic *B. vulgaris* extract (Meshkibaf et al., 2010).

3.4. Other Clinical Impacts

According to research on the preventative effects of aqueous *B. vulgaris* extract in Parkinson's disease models in rats, the extract can diminish the behavioural symptoms of the disease, most likely via inhibiting the ACE enzyme in brain tissue (Salar et al., 2010). By blocking specific indicators, two weeks of oral *B. vulgaris* use prevented mice from developing type 1 diabetes and inhibited the response of T cells (Cui et al., 2010). Inhibiting calcium oxalate crystal formation in renal tubules, reducing kidney oxidative stress and polyuria, and preventing weight loss in rats were all achieved with the use of *B. vulgaris* root extract mixed with water (Bashir, 2010). Plentiful antioxidants found in *B. vulgaris*, due to which it can play a vital role in promoting community health.In mice with streptomycin-induced hyperglycemia, aqueous *B. vulgaris* fruit extract significantly reduced the liver enzymes and total bilirubin while increasing the total serum protein. As a result, it is shown that *B. vulgaris* fruit may lessen diabetes mellitus-caused liver damage in diabetic mice via modifying detoxifying enzymes and antioxidants (Ashraf et al., 2013).

B. vulgaris extract has been shown to have the best effects on weight loss and a reduction in systolic and diastolic blood pressure. Large sample sizes in clinical trials allow for more accurate generalization of the results to the entire population, and this extract can be suggested for patients with alcoholic fatty liver who want to reduce their weight and blood pressure (SalehZadeh et al., 2013). Furthermore, administration of hydroalcoholic *B. vulgaris* extract to diabetic rats can result in a significant reduction in their lipid profile.

4. MEDICINAL USES OF *Taraxacum officinale*

The name "Taraxacum" comes from the Greek words "taraxos" (disorder) and "akos" (remedy), and the word "officinale" denotes a plant used in medicine. *Taraxacum officinale* is a perennial plant belonging to the family Asteraceae. It is found in Europe, Asia, and North America. It is a very common weed spreading in gardens, agricultural crops, pastures, and wasteland. Its common name is dandelion and its the member of the family Asteracewae. The root and the young tops are mainly used for medicinal purposes (Grieve, 1931). Due to their nutritional significance, *Taraxacum* *officinale*'s young leaves are frequently utilized in food as salads, beverages, and vegetable dishes. *Taraxacum officinale* leaves provide significant levels of fibre, minerals, vitamins, and vital fatty acids (Escudero et al., 2003).

4.1. Hepatoprotective Effects

Taraxacum officinale is beneficial for both treating and preventing complications with the liver. According to one study, the polysaccharides of this plant can effectively stop acetaminophen (APAP)-induced liver injury in a mouse model (Cai et al. 2017). According to a study, this plant's leaf extract possesses hepatoprotective properties against the toxicity of APAP (Colle et al. 2012). *Taraxacum officinale* leaves extract has been shown in other research to be effective in both the prevention and treatment of non-alcoholic fatty liver disease (Davaatseren et al., 2013). An earlier investigation revealed that this plant's leaf extract possesses hepatoprotective properties against in vivo liver injury brought on by sodium dichromate (Hfaiedh et al., 2016). The polysaccharides derived from this plant have been shown to have protective properties against liver damage *in vivo* in another study, which also discovered that *Taraxacum officinale* root aqueous extract can prevent alcohol-induced liver damage (Park et al., 2010).

4.2. Diuretic Activity and Treatment of Urological Diseases

Taraxacum officinale extracts were reported to exhibit diuretic action in a mouse model in a prior research investigation. (Râcz–Kotilla et al. 1974). In healthy people, this plant's ethanolic leaf extract enhances urine frequency and quantity of fluid excretion (Clare et al 2009). Two further trials revealed that *Taraxacum officinale* extract is effective in treating and preventing kidney illnesses including urolithiasis (Karakus et al. 2017).

4.3. Activity Against Colitis

Using *in vitro* and *in vivo* models, a study demonstrated that *Taraxacum officinale* root extract can have therapeutic effects in ulcerative colitis. (Ding and Wen, 2018). Another study discovered that using a mouse model, this plant can treat colitis. In this trial, a *Taraxacum officinale* extract appeared to prevent colitis more effectively than an anti-inflammatory medication. This plant's anti-oxidative, anti-inflammatory, and regenerative properties specifically averted colitis (Han et al., 2017). An earlier investigation discovered that a polysaccharide from *Taraxacum officinale* can treat ulcerative colitis (Wang et al., 2017). Another study showed that taraxasterol works well in vivo to cure acute colitis (Chen et al., 2019). So, by regulating fatty acid metabolism and dysbiosis, *Taraxacum officinale* extract can reduce the symptoms of colitis.

4.4. Effects on Immune System

According to earlier research, *Taraxacum officinale* extract strengthens the immune system by raising the production of nitric oxide (NO) and inflammatory mediators in mice (Kim et al. 1998; Lee et al. 2012). Another study found that taraxasterol can activate the Bax/Bc1-2 anti-apoptotic signalling pathway, which is downregulated in autoimmune diseases (Sang et al. 2019). Extracts of *Taraxacum officinale* improve the immunological response in living organisms (Tan et al2017).

4.5. Antiviral Activity

In vitro, aqueous *Taraxacum officinale* extract inhibits the replication and reverse transcription of HIV-1, demonstrating antiviral efficacy. The plant extract can stop the spread of the influenza virus, hence preventing infections. (He et al. 2011). Hepatitis B virüs is susceptible to the antiviral effects of taraxerol, a bioactive component found in taraxecum officinale extract (Yang et al. 2020). Serotype 2 of the dengue virus is susceptible to the plant extract's antiviral properties (Flores-Ocelotl et al., 2018). The extract aslo have efficacy against Hepatitis C virus (Rehman et al., 2016).

4.6. Antifungal Activity

The medicinal extract of the plant can disrupt cell wall of *Candida albicans* and hence shows effecacy against *Candida albicans* (Liang et al 2020).

4.7. Antiarthritic Activity

An earlier study demonstrated that the antiarthritic properties of taraxasterol from *Taraxacum officinale* by reducing inflammation *in vivo* (Wang et al. 2016).

4.8. Antibacterial Activity

Taraxacum officinale contains oligosaccharides and polysaccharides that have an antibacterial action on *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis* (Wang, 2014; Kenny et al., 2015). Another study discovered that the extract of *Taraxacum officinale* leaves is highly effective against *Staphylococcus aureus* and only moderately effective against gram positive and gram negative bacteria including *E.coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* (Diaz et al., 2018).

4.9. Antidiabetic Activity

Inhibition of -glucosidase and -amylase was the mechanism by which chemicals isolated from *Taraxacum officinale* produce hypoglycemic effects. (Choi et al., 2018). In an animal model, another study revealed that this plant possesses hypoglycemic qualities. This action may be brought about by an improvement in the insulin secretion of the -cells of the pancreatic islets. (Akhtar et al., 1985). Another study discovered that *Taraxacum officinale* leaf extract reduces insulin resistance and fasting blood glucose levels in living organisms (Davaatseren et al., 2013). *In vitro*, pancreatic beta-cells produce more insulin when treated with taraxacum officinale extract (Hussain et al., 2004).

4.10. Antiobesity Activity

One study found that *Taraxacum officinale* extracts are able to reduce body weight in a mouse model (Râcz–Kotilla et al., 1974). This plant can characteristicly reduce level of lipid in the body (Choi et al., 2010; Davaatseren et al., 2013) and *in vitro* (García-Carrasco et al., 2015). The extract have ability to stop the activity of pancreatic lipase (Zhang et al. 2008). The inhibition of pancreatic lipase resulted in hypolipidemic activity in the body (Aabideen et al.2020).

4.11. Antioxidant Activity

Taraxacum officinale posesses the antioxidant activity in the body oh the organism (Choi et al., 2010) also in the lebortory (Park et al., 2011). This plant's polysaccharides have been shown in two studies to exhibit *in vitro* antioxidant activity (Guo et al., 2019; Park et al., 2014). Other research showed that *Taraxacum officinale*'s polyphenols have antioxidant properties in cultured cells (Aabideen et al., 2020).

4.12. Anticancer Activity

There are anticancer properties in many cancer types for *Taraxacum officinale*. *Taraxacum officinale* extracts have been shown in one study to inhibit the invasion and proliferation of breast and prostate cancer cells. Another study showed that this plant extract can control the phosphatidylinositol 3-kinase (PI3K) /protein kinase B (AKT) pathway to decrease the proliferation and development of breast cancer cells (Sigstedt et al., 2008; Nassan et al., 2018). Studies conducted *in vivo* and *in vitro* revealed that this plant extracts can cause induce apoptosis in a variety of cancer cell types, including pancreatic, colorectal, prostate, and human leukemia cells. (Nguyen et al., 2019).

Taraxacum officinale has a number of beneficial effects, including diuretic, hepatoprotective, anticolitis, immunoprotective, antiviral, antifungal, antibacterial, antiarthritic, antidiabetic, antiobesity, antioxidant, and anticancer activities. The scientific literature frequently emphasizes *Taraxacum officinale*'s hepatoprotective, antioxidant, and anticancer effects as its therapeutic qualities. For the treatment and prevention of illnesses, this herb holds great promise.

5. MEDICINAL USES OF *Hydrastis Canadensis*

Hydrastis canadensis is a member of the Ranunculaceae family. Goldenseal, orange root, and yellow root are among popular names for Hydrastis. The medication is extracted from thick, yellow rhizome of the herb. It is native to North America and was brought to Europe in the 18th century. India is another country where its grown extensively (Tanna RS et al. 2020).

5.1. Hepatoprotection

In the homeopathic literature, it has been mentioned that *Hydrastis canadensis* can be quite beneficial in cases of liver cancer as well as inflammation of the lining of the liver. The medicinal extract of the *Hydrastis canadensis* can assist in treating the complicated liver disorders but there is no clinical evidence of a cure. There may be a sensation of bloating accompanied by a persistent dull pain in the vicinity of the liver. Jaundice developes that manifests as yellow complexion, dark yellow urine, pale feces and the mucous membranes turns yellow. There is inappetence, difficult breathing and pain on the palpation of liver. Additionally, the lining of the bile duct and gallbladder may become inflamed (Lin et al., 1937).

5.2. Effect on the Respiratory System

One of the most potent treatments for respiratory problems is hydrastis. It efficiently treats sinusitis-related issues such as Post Nasal Dripping (PND), inflammed mucous membranes of respiratory tract', coughing up loose expectoration (phlegm ejection), and inflammed turbinates. The mucous membranes in the sinuses and nasal passages are hyperactive and release more mucous than usual as a result clogging the nostrils and increasing discharges. By acting on these membranes, *Hydrastis canadensis* aids in reducing inflammation and controlling mucous secretion. When there are nasal discharges that feel burning and irritate the affected areas, *Hydrastis canadensis* can be helpful in treating such problems. In such circumstances, internal crusting forms in the nose. There is nasal discharge along with frontal headache. Turbinates, soft bones in the nasal cavity, are swollen, forcing to breathe through their mouths causing snoring while breathing (Johne et al. 2005). Tickling in the nose, especially in the right nostril, is one of this distinctive side effects of the medication. Recurrent episodes of sneezing, swelling around the eyes, and a dull headache in the frontal area that radiates to the arms are all symptoms in the patient. Bronchitis can also be treated with *Hydrastis canadensis*. The term "bronchitis" describes an inflammation of the air-transporting bronchial tubes. After the inflammation, the airway becomes constricted, which causes breathing problems, which this medicinal extract can successfully treat.

Elderly patients who experience such bronchitis bouts may also experience loss of appetite. That is taken care of by *Hydrastis canadensis*, which also reduces weakness and enhances breathing. This treatment is necessary for the recognizable "Old Man's Cough". *Hydrastis canadensis* can be helpful for people of all ages who have a tickling in the throat accompanied with a dry, strenuous cough or a loose cough that gets worse during the day with a thick, yellow, stringy mucus (Kumar et al., 2020).

5.3. Hydrastis for Ears

When the Eustachian tube isn't working properly, there may be postnasal discharge, ear blockage, and middle ear inflammation with a thick, persistent discharge that resembles pus. All of these symptoms respond favourably to hydrastis treatment. Along with these symptoms, there is also deafness in certain cases, and tinnitus, which are unusual noises in the ears, typically a roaring sound. It can also be administered if the tympanic membrane, or eardrum, has been perforated (Leyte et al., 2017).

5.4. Effect on the Gastro-Intestinal System

Stomach:

When there is a disturbance in the upper left part of the abdomen, *Hydrastis canadensis* is utilized to treat gastrointestinal conditions. The inability to adequately digest food results in inappetence. When it comes to treating stomach cancer, *Hydrastis canadensis* is a well-known treatment. When used with traditional medication, it works amazingly as an intercurrent therapy and can successfully manage symptoms. In cases of stomach cancer, the disease is typically asymptomatic at first (National Toxicology programe 2010). Patients frequently complain of chronic intermittent pain prior to the disease being diagnosed, which is typically at the "pre-cancerous stage." Then, the patient gradually starts to lose energy, stmach region become more sensitive, have decreased appetite and vomit frequently. It feels as though the meal merely lies in the abdomen and there is indigestion. Other symptoms include a coated tongue, acidic vomiting, and continuous acid production. It also have impact against Helacobacter Pylori (Mahady et al., 1999).

Rectum:

When the bowel movements are sluggish and the stool creation is thus delayed, hydrastis can cure chronic constipation. The patient skips days for evacuation of the stool from the body and and can only pass stool after taking laxatives. Small granules of stool may pass in the form of feces. There is constant straining while passing stool, to the point where the rectum begins to burn and hurt from the effort to get the gut empty. Sometimes, stool feels like it will pass, but when it is tried, only gas comes out. In addition, hemorrhoids (piles) can be treated with *Hydrastis canadensis* if the underlying reason is persistent constipation as previously mentioned or pregnancy. Possible symptoms include bleeding piles and severe weakness (Rabbani et al., 1987). During and after each bowel movement, there can be an unpleasant hemorrhoidal discharge, along with a burning discomfort in the anus. In cases of an anal fissure, constipation and persistent discharge, *Hydrastis canadensis* may also be effective. Excellent outcomes with this treatment have also been reported in cases of colorectal cancer (Lahiri et al., 1967).

5.5. Effect on Female Organs

In cases of leucorrhoea, uterine prolapse, uterine fibroids, congestive dysmenorrhoea, pelvic inflammatory disease, endometritis (inflammation of the endometrium), menopausal syndrome, and others, *Hydrastis canadensis* has demonstrated remarkable results. The medication has also shown therpaeutic impacts in cases of cervix cancer, uterine cancer, and breast cancer. By treating the eroded and ulcerated portions of the female reporoductive tract, hydrastis can assist in maintaining the normal lining of the mucosa. In addition to this, uterine abnormalities and lower back pain are well managed by this medicinal extract. The patient becomes feeble and anemic as a result of uterine hemorrhages and a prolonged menstrual cycle. The right iliac area is experiencing severe pain.In these patients, the leucorrhoea, or abnormal vaginal discharge, is typically highly persistent, thick, yellow in colour, and ropey in texture. Leucorrhoea is accompanied by severe itching. The pain is very severe and extend up to the shoulders and down the arms in the case of breast cancer. It is given in cases of scirrhous tumour of the breast, which is a solid, malignant tumour that grows slowly and has retracted nipples and enlarged lymph nodes in the axillary region (Messana et al., 1980).

6. MEDICINAL USES OF *Carduus marianus*

Carduus marianus belongs to the Compositae/Asteraceae family. Since the leaves of the plant have "milky veins," the plant is sometimes referred to as milk thistle and, in some other it is also known, *Cardus marianus*, *Marian thistle*, and *Mary thistle*. For more than 2000 years, silymarin has mostly been used to treat diseases of the liver and gallbladder like jaundice, hepatitis, and cirrhosis (Gazak et al., 2007). It is used to treat a variety of conditions including cancer, inflammation, and neurodegeneration, in addition to its liver-protective characteristics; outstanding antioxidant capability of this plant is primarily responsible for its broad pharmacological efficacy.

6.1. Treatment of Fatty liver

A disorder known as fatty liver occurs when the liver cells inappropriately store a lot of fat. People who consume too much alcohol or are obese are more likely to experience it. Scientific evidence is provided to support the usage of *Cardus marianus* in both people and animals by the variety of pharmacological activity it exhibits. The common molecular targets of CM include a variety of signalling pathways linked to oxidative stress and inflammation. The flavonolignans in CM are also potential PPAR and ABCA1 agonists, PTP1B inhibitors, and metal chelators. Its use relieves kidney, spleen, and liver congestion. It has been used to treat a variety of conditions, including amenorrhea, melaena, hemoptysis, hematuria, and uterine hemorrhage (Saad et al., 2006).

6.2. For Skin Protection and Treatment

Silymarin, a standardized extract from *Cardus marianus* seeds, has been studied for its dermatological application, specifically for its UVB-protective properties; however, information on *Cardus marianus* and its polyphenols effect on activity of enzymes participating in the (photo)aging process is limited. CM and flavonolignans exhibit anti-collagenase and anti-elastase activity. None of the flavonolignans or SM contain anti-hyaluronidase activity (Dixit et al., 2006).

6.3. Antidiabetic Effects

The effects of the plant extract on diabetes mellitus have been studied, and model animals and clinical trials have demonstrated that the extract lowers serum glucose levels. Although other mechanisms may also be involved, the protective effect of cardus marianus against pancreatic beta-cells is the primary explanation for this effect. It is already known that silymarin inhibits –amylase (Pandey et al., 2013).

Carduus marianus is an effective Liver Tonic and it shows the therapeutic impacts on multiple hepatic disorders including Jaundice, congection of liver, fatty liver, gall stones and also have therapeutic impacts on the other organs including congestion of spleen and kidneys, Amannorrhea, Hematuria, skin protection and anti diabetic effects. The plant extract having multiple therapeutic impacts make it not only beneficial for body of organism but also it is cost effective as the plant are genrally locally available and can be grown easily.

7. MEDICINAL USES OF *Aloe vera* (*Aloe barbadensis* miller.)

A perennial member of the Liliaceae family, aloe vera is a succulent plant that can withstand drought. The Arabic word "alloeh" or the Hebrew word "halal," which both indicate a bitter, shining substance, are the origins of the term aloe (Oxford Mediacl lebortory Manual). It has played a significant part in indigenous medical systems including ayurveda, siddha, unani, and homoeopathy throughout history. *Aloe vera* is the most potent and, hence, among the few kinds of *Aloe vera* that have been thought to be important commercially. *Aloe vera* is a potentially stemless or extremely short-stemmed plant that grows to be 60–100 cm tall and spreads through offset banches. With a few assortments emerging white bits on their upper and lower stem surfaces, the clears out are thick and plump, green to grey-green. The edges of leaf are having serrations that bear little white teeth. The blooms are produced in the summer on a spike that can reach a height of 90 cm. Each bloom has a pendulous shape and a yellow tubular corolla that is 2–3 cm long. *Aloe vera* forms arbuscular mycorrhiza, a favourable association that enables the plant to access mineral supplements much more effectively, like other Aloe species (Bunyapraphatsara et al., 2000).

Since more than 2000 years, aloe vera has been used in folk medicine. It is still a significant part of the traditional medicine of many modern countries, including China, India, the West Indies, and Japan. These succulent plants are xerophytes, which are plants that have evolved to live in environments with limited water availability and are distinguished by having a large water-holding tissue. The high water content of aloe vera plants, which ranges between 99 and 99.5%, is their distinguishing characteristic. Over 75 potentially active substances, including vitamins, minerals, enzymes, simple and complex polysaccharides, phenolic compounds, and organic acids, are said to be present in the remaining 0.5–1.0% solid material. It provides 19 of the 20 essential amino acids that human body needs, and these amino acids aid in the efficient operation of intricate enzyme system in the body. Antioxidants from aloe vera juice support the body's defences against free radicals. By reducing oxidative stress on your body, you minimise your risk of developing chronic diseases like diabetes, heart disease, and cancer. It cntains vitamins C, vitamins A, vitamin E, Beta-carotene, Folic acid acid, Calcium, Magnesium, eight calories, Just one gramme of protein, Under 1 gramme of fat ,3g of carbohydrates. Fibre: 2g and Under 1g Magnesium, an essential mineral for the usage of the nerves and muscles, is abundant in aloe vera juice. Over 300 separate enzyme processes, including those that control your blood pressure, are aided by magnesium in your body. Additionally, it influences how the heart beats. The solid components of aloe vera vary according to the origin of plant, species, climate, season, and farming practices. More than 400 different species of aloe are known, but only a few of these have been extensively utilised in the pharmaceutical and cosmetic industries. The most commonly used species of aloe are aloe barbadensis (Miller), also called aloe vera (Linne), aloe ferrox (Miller), and aloe perryi (Baker).

Most frequently used in the pharmaceutical sector is latex of the plant, a yellow juice derived from the pericyclic cells beneath the epidermial layer of the plant. Emodin, an anthraquinone found in latex, is a digestive irritant and cathartic. The inner central zone of the leaf contains mucilaginous cells with thin walls, which are used to make aloe gel. Because it contains a range of organic ingredients believed to contribute to the qualities of gel including as the alleged emollient, moisturising, and healing characteristics (Kahlo et al., 1999).

7.1. Topical Uses of Aloe Vera And Skin Care

The majority of the vitamins and amino acids required for skin healing are found in aloe vera. *Aloe vera* gel itself creates a glue-like substance on the skin that functions as a natural "band aid," trapping the nutrients and allowing them to start working right away while keeping out any bacteria or other agents that could slow down healing or stop it altogether. *Aloe vera* gel also contains a lot of water, which is necessary for the body to cure itself. *Aloe vera* is useful when added to topical formulations like ointments, creams, and lotions in addition to being effective when eaten orally. It mostly shields the wounds because of its moisturising qualities. Due of its astringent, moisturising, humidifying, and cleansing properties, aloe vera is frequently used in treating the issues related to dermatology. It smoothes out the wrinkles, softens the skin, and treats skin irritation, psoriasis, eczema, mycosis, red spots, herpes, psoriasis, and red spots. It also works well to remove and heal dead skin cells and skin that is brittle or sunburned. (Maenthaisong R et al., 2007).

7.2. Wound Healing

Three overlapping processes are thought to be involved in wound healing: matrix remodelling, new tissue creation, and inflammation (Choi S et at., 2003). The colourless gel from the parenchyma of the leaf is not only a powerful moisturising agent but also aids in the healing of skin lesions and reduces pain, it has been used to treat burns. Another study demonstrated the enhancement of burn wound healing (Garrastazu G et al., 2014). The *A. vera* gel extract facilitated quicker burn healing and restored the vascularity of the burn tissues. These outcomes resulted from a number of mechanisms, including acemannan's increased collagen production and rate of epithelization (Rodriguez MB et al., 1988).

7.3. Hepatoprotective effects

There have been research studies to suggest that Aloe vera has a hepatoprotective and an antifibrotic effect in animal models (Gupta et al., 2019). However, there has been some publicity recently which has linked *Aloe vera* products to potential liver damage with reports of hepatic liver inflammation and increased liver enzymes, measured on blood tests. While scientific studies have suggested that components of *Aloe vera* products (anthroquinones) may indeed be toxic, these have generally been linked to consumption of whole leaf products, rather than the refined, decolourised *Aloe vera* gel (Parlati et al., 2017).

The European Food Safety Authority (EFSA) has deemed that Aloe vera gel, created from the inner pulp of the skinned Aloe vera plant, is not harmful to drink if individual consumers do not exceed the recommended dosage, but have not recommended whole leaf products for human oral consumption (Andrade et al., 2018).

7.4. Anti Microbial Activity

It has been discovered that distinct *Aloe vera* extracts are effective against a variety of bacteria while individual components have varying anti-microbial properties (Cock Citation, 2008). The juice from cold-pressed *Aloe vera* leaves does show anti-microbial properties. (Alemdar et al., 2009). According to a comparison of *Aloe vera* leaf extracts in water, methanol, and acetone, the acetone extract exhibits the strongest growth-inhibitory effects on *Staphylococcus aureus* and *Escherichia coli*. Another study evaluated the inner gel of *Aloe vera* leaves from a 5-year-old plant against 14 patient-derived clinical strains and one reference strain of *Helicobacter pylori*. According to the findings, *Aloe vera* inner gel had MIC values against these 14 bacteria that ranged from 6.25 mg mL^{-1} to 800 mg mL^{-1}, which was comparable to other bactericidal species (Cellini et al., 2014).

7.5. Anti Diabetic and Antihypercholestremic Impact

Aloe vera is used to treat diabetes and its related symptoms, and diabetes is surely associated to high blood glucose levels (Hui et al., 2009). *Aloe vera* gel has been found in clinical investigations to have effects against hyperglycemia and hypercholesterolemia in people with type 2 diabetes (Pothuraju et al., 2016). *Aloe vera* gel also aids in enhancing glucose metabolism. For instance, a study found that *Aloe vera* gel can help improve the metabolism of obese people with diabetes and early, untreated diabetes by lowering body weight, body fat, fasting blood sugar, and fasting serum insulin levels. *Aloe vera* gel was used in a study to show that it not only had anti-diabetic benefits but also had cardioprotective activity because it helped STZ-induced diabetic rats by considerably reducing oxidative stress and improving their antioxidant state (Jain et al., 2010). Without having a substantial impact on liver or kidney function tests, acemannan significantly decreased fasting blood glucose and glycosilated haemoglobin levels. Given the findings of the trial, more research on the bioactivities and mechanisms underlying the anti-hyperglycemic effects of acemannan as well as additional clinical trials examining the efficacy and safety of aloe gel in the treatment of people with type 2 diabetes mellitus appear to be required.

7.6. Precautions to use Aloe vera

Researchers advise cautious using aloe vera on a regular basis. However, if the aloe vera product is free of aloin, a plant component that has been associated with colon cancer in rats, it might be safe to use as a topical sunburn cure. Between the aloe plant's outer leaf and its interior gel is where aloin is located.

7.7. Adverse Consequences

Aloe vera applied topically could irritate your skin. *Aloe vera* used orally might have a laxative effect and its prolog usage can result in cramps and diarrhoea. People who consume aloe vera for a prolonged period of time may experience electrolyte imbalances in their blood as a result of this. Additionally, colon can undergo staining by it, making a colonoscopy difficult to perform. Therefore, refrain from it atleast a month prior to a colonoscopy. Aloin, which can irritate the digestive tract, should not be present in aloe vera gel intended for topical or oral use (Longe et al., 2004).

Deep cuts and serious burns should not be treated with topical aloe vera. *Aloe vera* allergy is more common in people who are allergic to garlic, onions, or tulips. Oral *Aloe vera* at high dosages is harmful. If sombody have intestinal issues heart disease, haemorrhoids, kidney problems, diabetes, or electrolyte imbalances, then the oarticular group should avoid using aloe vera orally. *Aloe vera* supplements should not be taken orally by pregnant women and breastfeeding children due to a lack of data about their safety (National Toxicology Program).

7.8. Econnomical Significance of Medicinal plants

The wild plants exhibits intriguing characteristics with potential for commercial viability. Growing market demand for biologically active plant substances makes it more advantageous to cultivate medicinal plants rather than collect them from the wild. These advantages include consistent supply, standardized and enhanced manufacturing, and confidence of botanical identification. It is generally known that growth circumstances have a substantial impact on the amount of physiologically active components in the medicinal plants. Therefore, it's critical to evaluate the impact of cultivation methods (wild growth or organic farming) on the phytochemical makeup of *C. majus* populations. In addition to their impact upon health, cultivation of these plants can be a great business opprtunity for the farmers and as well as the traders. This will directly and indirectly support the economy of the farmers and ultimately the economy of the state.

8. CONCLUSION

Drug resistance is increasing day by day from past few years, pathogens are becoming resistant against the drugs previously used for the treatment so the incidence of treatment failure is increasing. Hence, there is an intense need of development of some alternative therapeutic approach that can be proved more effective in the treatment of certain diseases and herbal medicine can be a best alternative in this regard. In this chapter hepatoprotecive impacts of some plants, including *Chelidonium majus*, *Aelo vera*, *Carduus marianus*, *Hydrastis canadensis*, *Taraxacum officinale*, *Hydrastis canadensis* and *Berberis vulgaris*, is discussed alongwith other therapeutic impacts of these plants. As the herbal plants have holistic therapeutic approach, so the versatile therapeutic impacts of these plants are also discussed that mainly include wound healing, anti cancerous activity, Neurotonics, Anti inflammatory, immunomodulator, anti diabetic and the treatment of dermatitis. Care should be taken in the term if proper dosage of the active ingredients and the nature of active ingredients present in specific part of plant used for medicinal purpose.

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CHAPTER 12

ROSE (*Rosa hybrida*) PROPAGATION THROUGH TISSUE CULTURE

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INTRODUCTION

Roses, which are in the Rosa genus of the Rosaceae family and known as the queen of flowers due to their popularity and high aesthetic value, are one of the plants the most traded in the world; also, they are one of the most essential plants among the plants grown for their flowers (Nizamani et al., 2016; Harmon et al., 2022). Roses, which have been valued as both ornamental plants and fragrant plants since ancient times, are known as a crucial plant species used in different application areas such as perfume, cosmetics, aromatherapy, landscaping, medicine, and food sectors (Zlesak, 2007; Baydar, 2008). The rose, a northern hemisphere plant, originates from East Asia, and it is reported that the first cultivation of the plant began in China approximately 5000 years ago (Gülbağ et al., 2021). According to previous historical knowledge, rose oil and rose water in Türkiye were first produced in Bursa in 1885.

It has been reported that approximately 250 species of the Rosa genus, which grow both naturally and cultivated in our country, are emitted in the Northern Hemisphere (Özçelik and Koca, 2021). Roses spread a wide area and have been grown and cultivated from past to present with the elegant shapes of their flowers, attractive colours, pleasant scents, and numerous varieties (Bhattacharjee and Banerji, 2010).

With the expansion of genetic variation, five roses were called old European roses in the 18th century. Due to hybridisation studies carried out with these different rose classes in the 19th century, tea roses and roses called Hybrid Perpetual emerged. The hybrid tea rose (Rosa hybrida) class emerged by hybridising these roses in the mid-19th century. Hybrid Tea roses and Floribunda roses became the most common roses of the 20th century (Seyhan, 2020). The genealogy of roses is given in Figure 1. Although the term Rosa x hybrida is used today for modern roses, this expression does not indicate a species in the botanical sense.

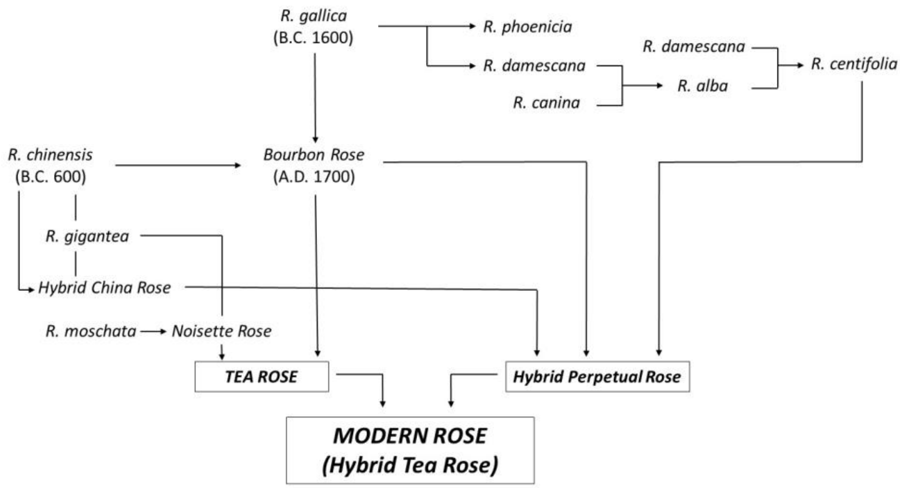

Figure 1: Genealogy of roses (Nakamura, 1987)

Thanks to their complex hybridisation histories, a wide variety of rose varieties have emerged, featuring diverse flower colours, shapes, and a multitude of distinct fragrances (Sadar et al., 2022; Tanjga et al., 2022). Because of the standard type of large and doubled flowers, shiny or semi-glossy leathery solid leaves, and long flower stems, Hybrid Tea roses, the most popular group with repeat blooming features, are especially preferred in the cut flower industry (Kılıç, 2020).

Different rose varieties are traded as cut flowers, park garden plants, and miniature potted plants (Khosh-Khui and Texteira da Silva, 2006). Cut roses were exported for $3,013,231,000, while imports of $3,460,061,000 were carried out according to worldwide 2022 data. The 1st, 2nd, and 3rd countries that ship the most cut roses worldwide are the Netherlands, Ecuador, and Kenya, respectively, while the 1st, 2nd, and 3rd countries that import the most roses are the U.S.A., the Netherlands, and Germany, respectively (Anonymous, 2022).

According to 2021 data, Turkey's income from exported ornamental plants was $130,171,792. Cut flowers took the largest share in exports with $59,447,229 and a rate of 45.67%. Turkey's import of cut flowers was $40,569,606, with $294,440 and a rate of 6.65% (TUİK, 2021).

According to 2022 data, ornamental plants were produced in 56,65.61 areas in Türkiye (TUIK, 2022). Cut flowers had the most production, with

15,170.75 areas among the production groups. When cut flower types are compared in the production area, cut rose ranked second with 2,736.40 production areas after carnation (6,416,714). The 1st, 2nd, 3rd, 4th, 5th, and 6th cities where it is produced were İzmir (788.00), Yalova (460,784), Bursa (433.500), Adana (405.200), Mersin (332.300), and Antalya (179.720), respectively (TUİK, 2022).

The world's cut flower industry changes yearly based on market orientation and consumer preferences. For these reasons, breeding companies are trying to develop various cut flower varieties with different colours, scents, shapes, and types and high yield and quality in cut flower production (Liorzou et al., 2016; Datta, 2018). In addition, the main aims of breeding studies on cut roses include vase life, suitability for transport, resistance to diseases and pests, thornlessness, and suitability for year-round production (Gülbağ et al., 2021). Classical breeding techniques such as hybridisation, mutation, haplodization, polyploidisation, and selection, and modern breeding methods such as gene transfer and genome editing technologies are used to create a new rose variety (Leus et al., 2018).

1. REPRODUCTION OF *Rosa hybrida* THROUGH TISSUE CULTURE

As one of the most important commercial flower crops used in the floriculture and cut flower industry worldwide, the rose is used in almost every activity in local and international markets. Traditionally, it is multiplied asexually through budding, grafting, or cuttings of scion cultivars onto specified rootstocks at seasons. These techniques are time-consuming and tedious, and their chances of success could be higher. Additionally, it has been noted that plants grown using these techniques often cause diseases that reduce flower quantity and quality, lowering their market value (Nizamani et al., 2016).

Susceptibility to diseases such as bacterial blight, black spot, and powdery mildew poses significant challenges to rose production. Many methods have been used to reproduce roses, including seeds, cuttings, layering, and grafting. Genetic diversity is possible through seed propagation, which is faster and more efficient than alternative approaches. Therefore, a novel method that is advantageous and appropriate for rose growth is required (Attia et al., 2012; Sadar et al., 2022).

Micropropagation is a technique used to propagate important varieties using aseptic tissue culture procedures. Techniques for tissue culture have been developed as prospective tools for quick and widespread plant species propagation. The most significant advantage of the in vitro propagation method is its tremendous multiplication power, which enables it to generate disease-free plants in a reasonably short amount of time, independently of seasonal factors, and in a financially advantageous way. Although vegetative propagation techniques, including cutting, layering, budding, and grafting, are widely used in the rose industry, they do not guarantee strong and disease-free plants. Propagation has been proven to be a highly effective approach for quickly propagating disease-free, uniform rose plants, and it may reduce propagation time and eliminate the need for grafting onto rootstocks (Nizamani et al., 2016; Afrin et al., 2022; Sadar et al., 2022). Utilising ten times less space than the conventional technique, a new plantlet can be produced in a short period after using a small amount of initial plant tissue. A virus- and disease-free plantlet, season-independent seedling supply throughout the year, the ability to grow challenging plants, such as particular breeds of roses, with greater success in tissue culture than with traditional methods can also be ensured by utilising tissue culture (Afrin et al., 2022; Harmon et al., 2022; Sadar et al., 2022). With the advantage of rapid proliferation in a short amount of time, in vitro culture techniques, which have recently become an alternative option for plant production, enable the year-round creation of healthy, virus-free plants (Skirvin et al., 1990; Yan et al., 1996, Rout et al., 1999, Pati et al., 2006). Tissue culture techniques have been used to produce and propagate roses since 1945 when Nobecourt and Kofler successfully got calli and roots from explant buds. The first-time embryo culture was applied to the production of roses was by Lamments in 1946. Martin (1985) showed that up to 400,000 plants could be cloned from a single rose throughout a year). This study was recorded as one of the early investigations using in vitro techniques.

The genotypes used in the numerous investigations carried out to now have been found to respond quite differently to in vitro reproduction and shoot formation capabilities. The ability for shoot formation is also influenced by explant type, variety, medium used, and hormone combinations. Table 1 lists some tissue culture research on the Rosa hybrida species between 1979 and 2003. The cultivars explant types, growth regulators, and combinations used for *R. hybrida*'s in vitro propagation, and the outcomes are briefly listed in the table.

Table 1: Brief descriptions of various in vitro propagation research on *Rosa hybrida* species conducted between 1979 and 2003

Literature Variety Explant	Purpose	Culture conditions	Results
• **Hasegawa et al., 1979** • **Improved Blaze cultivar** • **Shoot tip and lateral bud culture.**	• Shoot formation • Shoot formation according to explant type • Rooting	• **For shoot Formation:** • MS + (3 and 10 mgL^{-1}) BA+ (0, 0.3 or 3.0 mgL^{-1}) IAA combinations, • **For shoot formation according to explant type:** • Terminal shoot tips and lateral buds, • To identify differences MS+ 3 mgL^{-1} BA+ 0.3 mgL^{-1} IAA medium, • **For Rooting:** • MS+2 mgL^{-1} BA+0,3 mgL^{-1} IAA medium was used. • pH: 5.7 • Temperature: 26°C • Photoperiod: 16/8 hours	• **Shoot Formation:** Medium with maximum shoot formation: MS+ 3 mgL^{-1} BA+0.3 mgL^{-1} IAA (8 weeks, 3-fold proliferation/subculture). At the end of the 8th and 12th weeks, the number of proliferating shoots was determined, and an approximately 6-fold proliferation was observed (5.9 ± 0.6 shoot/culture per week and 5.9 ± 1.0 shoot/culture for 12 weeks). However, at the end of the 12th week, it was determined that the cultures visibly degenerated, and the number of senescent leaves increased. • **For the explant type:** It was observed that both terminal shoot tips and lateral buds produced equal numbers of shoots, and auxins did not make any difference in shoot proliferation. • **Rooting:** The rooting success rate was approximately %50,

			and the medium composition is MS+2 mgL^{-1} BA+0.3 mgL^{-1} IAA.
• **Skirvin and Chu, 1979** • **Forever Yours cultivar,** • **Shoot tip culture.**	• Shoot formation • Rooting	• **For Shoot Formation:** • MS+2mgL^{-1} BA +0.1mgL^{-1} NAA • MS+ Staba vitamins • LS (Linsmaier and Skoog, 1965) + 2 mgL^{-1} BA+0.1 mgL^{-1} NAA mediums, • **For Rooting:** • Hormone-free MS medium • MS+ (0,1, 1, 2, 3 and 4 mgL^{-1} NAA) • ¼ strength MS medium was used. • pH: 5.7 • Temperature: 23°C. • Photoperiod: 16/8	• **Shoot Formation:** Approximately 25% of the shoot tips planted in MS+2 mgL^{-1} BAP+0.1 mgL^{-1} NAA medium and approximately 20% planted in LS medium developed multiple shoots from axillary buds within five weeks. • **Rooting:** ¼ strength hormone-free MS medium gave the best results (3-week duration, 68%). Rooting success was determined as 11-20% (3-week period) in MS medium supplemented with 1-3 mgL^{-1} NAA.
• **Hasegawa et al., 1980,** • **Improved Blaze cultivar,** • **Shoot tip culture.**	• Shoot formation • Rooting	• **For Shoot Formation:** • All explants were cultured in MS+3 mgL^{-1} BA+0.3 mgL^{-1} IAA medium. • Different concentrations (0, 0.3, 1, 3, 10, and 30 mgL^{-1}) of three cytokinins (BA, N6-isopentenyladenine (2iP) and N6-furfuryladenine (Kinetin), • Combinations of these containing 0.3 mgL^{-1} IAA, • MS medium containing 1.0 and	• **Shoot Formation:** The increase in the applied BA concentration caused a decrease in shoot elongation. While 3, 10, and 30 mgL^{-1} 2iP application supports shoot formation, Kinetin had almost no effect on shoot proliferation. The combination of 1 mgL^{-1} BA+1 mgL^{-1} IAA supported shoot elongation. A slight increase in shoot elongation was observed in combinations of 3.0 mgL^{-1} BA+ 0.3-3 mgL^{-1} IAA.

		3.0 mgL^{-1} BA for comparison in Kinetin and 2iP applications, • Auxin IAA was combined with 0, 0.1, 0.3, 1, 3 and 10 mgL^{-1} concentrations in environments containing 1.0 or 3.0 mgL^{-1} BA. • In terms of its effects on shoot proliferation, gibberellic acid (GA_3- 0, 0.1, 0.3, 1, 3, 10, 30, and 100 mgL^{-1}), adenine sulfate- dihydrate (0, 10, 30, 100, and 1000 mgL^{-1}) and $NaH_2PO_4H_2O$ (0, 10, 30, 100, 300 and 1000 mgL^{-1}) were added. • **For Rooting:** • Shoots with a length between 2-10 mm were used, and root formation was evaluated after 10-14 days. • Root formation success was examined in plants grown in media containing three different auxins (NAA, IAA and IBA). • Auxins; 0.03, 0.1, 0.3, 1.0, 3.0, 10.0, 30.0 mgL^{-1} NAA; 1.0, 30.0 mgL^{-1} IAA; 0.1 and 1.0 mgL^{-1} IBA.	All applied GA_3 concentrations inhibited shoot proliferation. As GA_3 concentration increased, the size of the deformation also increased. • **Rooting:** Application of 0.03 and 0.10 mgL^{-1} NAA increased the success of rooting and transplantation, but a sharp decrease was observed with more than 0.10 mgL-1 concentration. In terms of rooting, 1.0 mgL^{-1} IAA was equally good as best NAA practices; 0.1 mgL^{-1} IBA revealed almost the same effects as the control. Shoot elongation and leaf expansion were determined to be maximum at 0 and 0.03 mgL^{-1} NAA. Reducing the salt concentrations in the MS nutrient medium by ½ or ¼ stimulated root formation and post-transplant viability. Increasing these concentrations two-fold prevented root formation. Signs of deterioration, which are manifested by aging in the leaves, appeared on the shoot tips kept in a medium

		• pH: 5.7 • Temperature: 26°C • Photoperiod: 16/8 hours	containing no cytokinin for more than 14 days. Additionally, extending the culture period significantly reduced the success of transfer to soil.
• **Khos-Khui and Sink, 1982** • **Bridal Pink cultivar** • **Shoot tip culture**	• Effect of different auxin sources and concentrations on rooting. • Effect of temperature change on rooting	• **For Rooting:** • The effect of different auxin sources (NAA, IBA, IAA), concentrations, and, combinations (0; 0.025; 0.05; 0.1 mgL^{-1}) on rooting was examined. • The effect of these NAA/IAA and NAA/IBA combinations at 0.1 mgL^{-1} concentrations on root formation quality was investigated. • Temperature gradient experiments consisted of: (1) 1 week of culture at 5°C, followed by 1 week of culture at 22 + 2°C; (2) culture at 25± 2°C for 1 week, followed by the same temperature for 4 days at 5°C; (3) 4 days culture at 5°C, 3 days culture at 25 + 2°C, 3 days at 5°C and the rest at 25 +	• **Rooting:** Rooting was observed at a rate of 71% in plants where 0.05 and 0.10 mgL^{-1} NAA were applied together. While indolebutyric acid (IBA) alone could not stimulate rooting, it was observed that Indoleacetic Acid (IAA) and Naphthaleneacetic Acid (NAA) applications stimulated rooting. Both NAA+IBA and NAA+IAA combinations were equally effective in stimulating rooting, and IAA alone increased rooting more than IBA or NAA. Considering the quality of the resulting roots, it was determined that the NAA + IBA combination gave better results than the NAA + IAA combination. • **Effect of temperature changes:** Growing the cultures at 5°C for 1 week and then transferring them to room temperature increased the rooting percentage and the root growth, i.e., the

		2°C. • pH: 5.8 • Temperature: 25± 2°C, • Photoperiod:-	rooting percentage of the control, from 58% to 70%. No significant change was observed in other applications. The best medium combination for acclimating rooted explants to outdoor conditions was 0.1 mgL^{-1} IAA or 0.05 mgL^{-1} IBA. Of the plants, 94% and 90% were successfully acclimated, respectively.
• **Rout et al., 1989** • **Landora cultivar** • **Single axillary bud culture.**	• Shoot Formation • Rooting	• **For Shoot Formation:** • MS • MS+ (0.25, 0.5, 1 mg L^{-1}) BAP combinations, • MS+ 0.25 mg L^{-1} BAP+(0.25, 0.5 mg L^{-1}) GA_3 combinations, • MS+ 0.5 mg L^{-1} BAP+(0.25, 0.5 mg L^{-1}) GA_3 combinations, • **For Rooting:** • MS • MS+ (0.25, 0.5, 1 mg L^{-1}) NAA combinations, • MS+ (0.25, 0.5, 1 mg L^{-1}) 2,4-D combinations, • MS+ (0.25, 0.5, 1 mg L^{-1}) NAA+0.1 mg L^{-1} 2,4-D combinations were used. • pH: 5.8 • Temperature: 25± 2°C, • Photoperiod:14/10	• **Shoot Formation:** Maximum shoot formation (5.25±0.92) occurred in the combination of MS+ 0.25 mg L^{-1} BAP+0.25 mg L^{-1} GA_3. • **Rooting:** Maximum rooting occurred (6.00± 0.81) in the combination of MS+ 0.25 mg L^{-1} NAA+0.1 mg L^{-1} 2,4-D.

		hours. • 3.000 lux light intensity	
• **Burger et al.,1990** • **Bridal Pink and Amorous cultivars** • **Excised embryos of crosses between flowering plants of genotypes and several pollen parents**	• In vitro reproduction from excised embryos shoot formation. • Callus Formation	• **For Shoot Formation:** • ½ MS + 1.0 µM BA+0.05 µM NAA medium; • **For Callus Formation:** • ½ MS + 0.8 µM biotin+2.7 µM riboflavin+5.7 µM askorbic acid+ 7.2 µM koline cloride+8.3 µM sisteine+87.6mM sucrose + % 0.6 Phytagar medium was used. • pH: 5.8 • Temperature: 27 °C • Photoperiod:16/8 hours	• **Callus Formation:** Explanted embryogenic tissues were grown in ½ MS + 1.0 µM BA + 0.05 µM NAA medium for several months, and well-developed shoots were separated and grown individually and then taken for rooting in a medium containing 1 µM IBA without BA or NAA. • **Adventitious Shoot Formation:** It also occurred from organogenic calli taken 21-35 days after pollination from plants rooted in the greenhouse. • **Histological examination** of normally developing embryos has shown that well-defined embryonic axes begin to develop approximately 20-25 days after pollination. When plant populations from different crosses were analyzed, differences in flowers were observed.
• **Rout et al., 1991** • **Landora cultivar.** • **Leaf and stem explant**	• Callus formation from leaf explant • Callus formation from stem explant • Stimulation of somatic embryogen	• **For Callus Formation from Leaf Explant:** • ½ MS+ 2.2µM BA+ 5.4 µM NAA + 2.2µM-9.0 µM 2,4-D medium, • **For Callus Formation from Stem Explant:** • ½ MS+ 2.2µM	• **Callus formation:** ½ MS + 2.2 µM BA + 0.05 µM NAA + 0.3 µM GA_3+ 200-800 mgL^{-1} L-proline at the end of 8 weeks in the environment, embryogenic callus and then somatic embryos were formed.

	esis from callus	BA+ 5.4 µM NAA+9.0 µM 2,4-D medium used. • **For Inducing Somatic Embryogenesis from Callus:** • Calluses were transferred to medium containing ½ MS +2.2 µM BA, 0.05 µM NAA, 0.3 µM GA_3, and 0-800 mgL^{-1} L-proline. • Calli incubated at 25±2°C in the growth chamber were grown either in continuous darkness or under cool white, fluorescent light (50/xmol $m^{-2}s^{-1}$) for 16 hours per day for induction of somatic embryogenesis. • For somatic embryo germination, embryogenic cultures were stored in the refrigerator at 8±1°C for 2-7 days before separation of somatic embryos and inoculation in regeneration medium. • pH: 5.7 • Temperature: 21±1°C • Photoperiod:16/8 hours	Repeated subcultures for embryogenic callus formation in an L-proline-free medium were maintained for 16 months. Approximately 12% of cotyledon stage embryos were taken from cultures, cold stored at 8 °C for 4 days, and germinated in 1 MS + 2.2/zM BA + 0.3/ µM GA_3 + 24.7 µM Adenine sulfate medium.

• **Hameed et al.,1993** • **Diamond Jubly and Lans France cultivar.** • **Capitulum explant**	• Callus Formation	• **For Callus Formation:** • 0.5 mgL^{-1} 2,4-D + (0, 0.1, 0.5, 1.0, 1.5, and 2.0 mgL^{-1}) Kin • 250mgL^{-1} Sodiumdiethyldithiacarbamate (SDC) was also added to the nutrient medium as an antioxidant substance. • pH: 5.7 • Temperature: 26±1°C • Photoperiod: 16/8 hours	• **Callus Formation:** Between the two varieties, more callus formation and growth ratio were observed in the Diamond Jubly variety in all media. The optimum growth medium for the Diamond Jubly variety was determined as 0.5 mgL^{-1} 2,4-D + 0.1 mgL^{-1} Kin. Optimum growth was observed in the Lans France variety in 0.5 mgL^{-1} 2,4-D+0.5 mgL^{-1} Kin medium. 250 mgL^{-1} SDC added to both media as an antioxidant effectively controlled browning in the cultures of both varieties.
• **Van der Salm et al., 1994** • **Moneyway cultivar** • **Nodal eksplant**	• Shoot formation from nodal explants in 3 different mediums.	• **For Shoot Formation:** • Tissue culture material of 'Moneyway' rose rootstock was obtained from axillary shoots and the classical disinfection method was followed. • Explants were planted in Murashige and Skoog (MS), Quoirin and Lepoivre (QL), and Woody Plant Medium (WPM) growth media. • Growing shoots	• **Shoot Formation:** At the end of the 6-week period, growth, as determined by shoot length, was faster in MS and QL than in WPM. Although growth was better, chlorosis occurred in the newly formed leaves starting from the third week. This situation is associated with the lower chlorophyll content of the shoots. Replacement of FeEDTA with FeEDDHA in QL and MS media resulted in the development of green leafy shoots even after 3

		were subcultured every 6 weeks. • MS, QL, and WPM media containing 86 μM FeEDTA or FeEDDHA, 58.4 mM sucrose, 4.4 μM BA, 0.49 μM IBA, and 0.8% (w/v) agar (Oxoid, bacteriological agar) were used for subculture: • Experiments were carried out with a randomized block design. • pH: 5.6 • Temperature:22°C. • Photoperiod: 16/8 hours. Illuminated by Osram L58W/77 fluorescent tubes).	months. It has been suggested that FeEDDHA is a more photostable chelate than FeEDTA, resulting in higher iron availability to rose shoots. The effect of the iron chelate formula on the micropropagation of plant species sensitive to iron deficiency is discussed.
• **Marchant et al., 1996** • **Trumpeter and Glad Tidings cultivars** • **Root and petiol explant.**	• Callus Formation • Maturation and germination of the embryo • Shoot Multiplication	• **For Callus Formation:** • MS+ 1 mg L^{-1} BAP + 0.1 mg L^{-1} GA_3 + 0.04 mg L^{-1} NAA. • **For Embrio Maturation:** • MS + 1 mg L^{-1} 2,4-D + 1 mg L^{-1} ABA + 0,3 mg L^{-1} GA with proline (0, 300 or 600 mg L^{-1}). • **For Embrio Germination:** • MS + (0, 0.5 or 1 mgL^{-1}) BAP+0.1 mg L^{-1} IBA+ Maltoz medium. • **For Shoot Formation:**	Callus was formed from leaf and petiole explants of both varieties within 10 days. The medium in which 18% (lowest) abnormal embryo formation was observed in the Trumpeter variety was mixed with MS + 1 mgL^{-1} 2,4-D + 1 mgL^{-1} ABA + 0.3 mgL^{-1} GA or 600 mgL^{-1} Contains proline. Medium with 12% (lowest) abnormal embryo formation in the Glad-tidings genotype with MS + 1 mgL^{-1} 2,4-D + 1 mgL^{-1} ABA + 0.3 mgL^{-1} GA or 300 mgL^{-1} contains 1 proline. When proline was not

		• MS + (0, 0.5 or 1 mg L^{-1}) BAP+0.1 mg L^{-1} NAA medium was used. • pH: 5,8 • Temperature: 23±3°C • First 14 days of darkness, then 28 days of 16-hour photoperiod.	added to the embryo maturation media of both genotypes (0 mgL^{-1}), fewer abnormal embryos were formed. At the end of the study, phenotypically normal plants were recovered from germinated somatic embryos and successfully transferred to the greenhouse for flowering.
• **Kapchina and Toteva, 2002** • **cultivars** • **Single-node culture**	• Examining the effects of two cytokinin antagonists (**ACK1** and **ACK2**) on *in-vitro* plant growth.	• **To determine the effect of the cytokinin antagonist:** • The presence of two different cytokinin antagonists (ACK1: 2-chloro-4-cyclobutyl-amino-6-ethylamino-1,3,5-triazine and ACK2:N-(4-pyridyl) in single node explants of two *Rosa hybrida* varieties with different apical dominance. The effects of -O-(4-chlorophenyl) carbamate) on in vitro plant growth were examined. • MS+2.2 µM BA • MS+10 µM ACK1 • MS+10 µM ACK2 mediums were used. • Temperature: 22 °C • Photoperiod:16/8 hours	• **The effect of the cytokinin antagonist** It reduced the number of buds sprouting to varying degrees in both varieties. It has been determined that the effect varies depending on both the applied concentration and duration.

• **Kim et al., 2003a** • **4th of July, Tournament of Roses, Graham Thomas and Sequoia Ruby cultivars** • **Axillary and bud culture.**	• Shoot Formation • Callus Formation	• **For Shoot Formation:** • MS + 0.5 mg L^{-1} BA medium, every four weeks, shoot clusters were separated from each other and turned into separate shoots. • **For Callus Formation:** • MS + (0.1, 0.5, 1, 2 mgL^{-1}) 2,4-D. or MS + (0.1, 0.5, 1, 2mgL^{-1}) NAA • MS + (0.5-5 mgL^{-1}) BA+ (2 and 4 mg L^{-1}) Kinetin + Zeatin + TDZ + 0.1 mg L^{-1} NAA • MS + 0.25 mgL^{-1} NAA+1.5 mgL^{-1} Zeatin+1.5 mgL^{-1} GA_3 combinations were used. • pH: 5,8 • Photoperiod:16/8 hours.	The 4th of July cultivar showed the highest regeneration frequency in the medium where 1 mgL^{-1} NAA was applied. This was followed in a medium containing 4 mg L^{-1} zeatin. To stimulate somatic embryogenesis, explants were planted in MS basal medium (0.5-5 mg L^{-1}) BA, Kinetin, Zeatin and TDZ medium. After 4 weeks, it was determined that the most suitable environment for the germination of 50 randomly selected embryos from each application group was MS + 1 mg L^{-1} BA. It has been reported that the most suitable environment for stimulation and proliferation of somatic embryogenesis is MS + 4 mg L^{-1} Zeatin.

Studies on somatic embryogenesis of roses began in the early 1990s (Roberts et al., 1995). Studies on the induction of somatic embryogenesis have been conducted using a range of explants, including internodes (Rout et al., 1991; Arene et al., 1993; Hsia and Korban 1996; Dohm et al., 2001), leaves (De Wit et al., 1990; Rout et al., 1991; Arene et al., 1993; Hsia and Korban 1996; Visessuwan et al., 1997; Kintzios et al., 1999; Dohm et al., 2001; Li et al., 2002; Kim et al., 2004; Estabrooks et al., 2007; Vergne et al., 2010), petioles (Marchant et al., 1996; Estabrooks et al., 2007), roots (Arene et al., 1993; Marchant et al., 1996; Van der Salm et al., 1996; Sarasan et al., 2001), petals (Murali et al., 1996), filaments (Noriega and Sondahl, 1991), and immature seeds (Arene et al., 1993; Kunitake et al., 1993; Kim et al., 2003b). Numerous studies also highlight the significance of the genetic component for callus development in roses (Hsia and Korban, 1996; Kintzios et al., 1999; Nguyen et al., 2020).

During tissue culture studies, it is crucial to administer hormones to the plant at the appropriate time. Two important hormone classes used in these studies are cytokinins and auxins. These hormones promote cell division, elongation and differentiation, and subsequent stems, leaves, and roots development. It is necessary to apply hormones with different properties to the developing plant at other times because a hormone that promotes stem and leaf development may inhibit root formation (Hyndman et al., 1982). Auxins (indole-3-acetic acid (IAA), 2,4-dichloropenoxyacetic acid (2,4-D)), which play an essential role in regenerative callus production in roses, are reported to be most widely used in regeneration, primarily through somatic embryogenesis (Shen et al., 2016). Some cytokinins commonly used for rose regeneration include zeatin (Ludwig-Müller 2000; Vergne et al., 2010; Zakizadeh et al., 2008), kinetin (Cai et al., 2022; De Wit et al., 1990), 6 - benzylaminopurine (BAP) (Hsia and Korban, 1996), and thidiazuron (TDZ) (Cai et al., 2022; Chen et al., 2014; Li et al., 2002; Zakizadeh et al., 2008). BAP, a synthetic cytokinin that stimulates growth and cell division, has been widely used in rose micropropagation studies to stimulate axillary shoot proliferation and regeneration (Katsumoto et al., 2007; Kim et al., 2004).

In the study conducted by Khosravi et al. (2007), 6-Benzylaminopurine (BAP) (0, 2, 4 and 8 µM) and 1-Naphtalene acetic acid (NAA) (0, 0.05, 0.25 and 0.5 µM) in Van der Salm (VS) medium was used to optimize in vitro propagation of *Rosa hybrida* cv. Iceberg. As a result of the study, it was determined that as the concentration of BAP increased, the growth rate increased in all NAA concentrations used. In a medium containing 4 µM BAP + 0.5 µM NAA, a 10-fold increase was obtained with a maximum number of axillary shoots (10.1) and new leaves per explant (25). Shoots from in vitro tests were transplanted to full, 1/2, and 1/4 strength semi-solid and liquid VS media for rooting experiments. It was reported that the best root growth was obtained in the semi-solid medium at ¼ strength. In the last stage of the study, the regenerated plantlets were transferred to the soil, and it was determined that the survival rate of the rooted plantlets transferred to the soil varied between 70% and 90%.

It was reported that MS (Murashige and Skoog, 1962) culture medium containing 0.5 mgL^{-1} BAP + 0.25 mgL^{-1} GA3 + 0.01 mgL^{-1} IAA (Murashige and Skoog, 1962) used in the in vitro propagation study using axillary buds of Vegas cultivar of *Rosa* × *hybrida* as explant source was the growth medium with the best growth rate (Drefahl et al., 2007).

In the study investigating the effect of growth regulators, photoperiod, gelling agents, and subculture period for the micropropagation of hybrid roses, 3 different *Rosa hybrida* cultivars (Cri Cri, Pariser Charme and First Red) were used. Explants were cultured in MS medium containing 6-benzyl-aminopurine (BA) (0, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5 mgL^{-1}), kinetin (0, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5 mgL^{-1}), indole-3-acetic acid (IAA), and 1-naphthalene acetic acid (NAA) (0, 0.1, 0.25, 0.5 mgL^{-1}). Including Indole-3-Acetic Acid (IAA; 0.1-0.25 mgL^{-1}) in cytokinin-rich medium encouraged shoot proliferation; 16-hour photoperiod increased proliferation in all treatments; the highest proliferation frequency was up to the 6th and 7th subcultures. It was also reported that rooting success was easily achieved in ½ MS medium supplemented with 0.25 mgL^{-1} IBA (indole-3-butyric acid) and 2% sucrose and that the plants acclimatised to external conditions grew normally and flowered about one month after the transfer (Senapati and Rout, 2008).

Attia et al. (2012) used axillary buds containing nodal segments of Al-Taif Roses, a local variety of *Rosa hybrida* L. cultivated in Egypt, as explants. After that, these buds were cultured on a solid MS medium with varying concentrations of Benzylaminopurine (BAP, 1, 2, and 3 mgL^{-1}) combined with 1 mgL^{-1} of Kinetin (Kn). The study investigated the impact of different concentrations and combinations of indole-3-acetic acid (IAA) and indole-3-butyric acid (IBA) on shoot and root development. The results showed that the highest shoot formation percentage (85%) was achieved in the 2 mgL^{-1} BAP + 1 mgL^{-1} Kn medium, while the highest rooting rate (66.7%) was observed when the MS medium was supplemented with 2 mgL^{-1} IBA.

In a study involving vegetative (leaves, stems, leaf petioles) and flower (petals, pistils, stamens) explants of both *R. hybrida* and *R. gallica*, the influence of different combinations of 2,4-dichlorophenoxyacetic acid (2,4-D), 6-benzylaminopurine (BAP), and gibberellic acid (GA) on callus formation was researched (Tarrahi and Rezanejad, 2013). The highest callus formation was achieved with 2 and 3 mgL^{-1} of 2,4-D + 1 mgL^{-1} BAP. While stem explants of *R. gallica* initiated callus formation at the end of the 4th day, other *R. gallica* and all of *R. hybrida* had the highest percentage of callus initiation at the end of the 8th day. Both species exhibited a higher callus growth rate in leaf and stem explants. The highest callus volume in both species was obtained from vegetative explants after 2 months and flower explants after 2.5 months. Subsequently, the anthocyanin and chlorophyll levels of the calli were examined and yielded different values depending on the species and the type of explants in this study. The results revealed a notable difference between the two species: calli obtained from vegetative explants of *R. gallica* exhibited higher anthocyanin content, while in *R. hybrida*, a higher concentration of chlorophyll was observed (Tarrahi and Rezanejad, 2013).

The effects of plant growth regulators applied at different concentrations in stem explants were investigated to optimise indirect regeneration and direct regeneration of *Rosa hybrida* cultivars "Apollo, Black Baccara, Maroussia, and Amanda". In indirect regeneration, it was determined that the highest callus production occurred with the application of 10 µM (2,4-D). The highest regeneration frequency was achieved when calli were transferred to an MS growth medium containing 2.5 µM TDZ and two µM gibberellic acid. Across all four varieties using stem explants in the experiments, it was observed that the regeneration frequency was higher in direct regeneration compared to indirect regeneration. Furthermore, it was noted that in the case of direct regeneration, the appearance of new shoots happened at an earlier stage (Pourhosseini et al., 2012).

In a study conducted by Ram et al. (2013), calli obtained from the Pusa Ajay variety of *Rosa hybrida* were used to investigate the effects of Salicylic Acid (SA) and Methyl Jasmonate (MeJA) on both pigment content and pigment production. Leaf explants were cultured in an MS medium containing IBA, kinetin, and adenine sulfate and were subcultured at 21-day intervals to establish stock callus cultures. A modified Euphorbia millii medium was employed for anthocyanin induction, supplemented with 204.5 mM sucrose, 2.45 µM IBA (indole butyric acid), and 2.33 µM kinetin. SA and MeJA were applied in different concentrations and combinations (100 µM SA + 0.05 µM MeJA, 200 µM SA + 0.50 µM MeJA, and 400 µM SA + 5.00 µM MeJA) in Euphorbia millii medium was investigated. The obtained data indicate that this application positively impacted both callus biomass and anthocyanin accumulation (Ram et al., 2013).

Bayanati et al. (2015) researched to enhance the micropropagation of the "Black Baccarat" variety of *Rosa hybrida*. They employed an in vitro propagation technique that holds significant importance in efficiently propagating varieties possessing desired characteristics while ensuring the production of disease-free and healthy plants. Nodal segments were cultured in liquid and solid media (MS, VS, and WPM). The results indicated that the highest shoot proliferation occurred in the VS medium, with the highest proliferation rate and growth rate observed in the liquid medium. A VS growth medium containing NAA (0.5 μM) along with three different mineral salt concentrations was used for root formation. The experiments revealed that the mineral salt concentration influenced root formation with the highest number of roots obtained in the semi-solid and 1/4 strength VS medium (Bayanati et al., 2015).

Nizamani et al. (2016) used nodal meristem explants to identify appropriate basal media and growth regulators for the in vitro propagation of *Rosa hybrida*. Stem formation was observed by adding BAP, IBA, and NAA at different concentrations and combinations to the MS growth medium. In contrast, root formation was observed by adding NAA and IBA at various concentrations and combinations to the ½ strength MS growth medium. The research results indicated that parameters such as initiation days, shoot count, shoot length, leaf count, root count, and root length were statistically significant. It was reported that the best stem induction combination was MS+0.1 mgL^{-1} NAA+2 mgL^{-1} BAP, and the best root induction combination was ½ MS+2 mgL^{-1} IBA.

The study conducted by Harmon et al. (2022) aimed to develop in vitro regeneration protocols for three selected rose varieties (Chewnicebell, Bucbi, and Cheweyesup). Explants from leaf tissues were used for callus formation, and various combinations and concentrations of auxins (2,4-D and 2,4,5-T), carbohydrates (fructose, glucose, and sucrose), and cytokinins (TDZ and BAP) were employed. The best regenerative calli were obtained in the Chewnicebell variety (40%) with a medium containing 10 μM 2,4-D and 30 gL^{-1} sucrose, in the Bucbi variety (24%) with 10 μM 2,4-D and 60 gL^{-1} glucose, and in Cheweyesup variety (32%) with 5 μM 2,4-D and 30 gL^{-1}

sucrose. The results highlighted genotype-dependent variations, and all obtained plantlets were acclimated to external conditions and transferred to soil.

2. DETERMINING THE EFFECT OF DIFFERENT GROWTH MEDIA ON THE PRODUCTION OF *Rosa hybrida* BY TISSUE CULTURE

In order to carry out a successful micropropagation study, there are stages, each of which has its own importance. These stages are, respectively (1) initiation of aseptic cultures, (2) multiplication of shoots, (3) rooting of micro shoots, and (4) strengthening of plants grown with tissue culture and transferring them to the natural area. For the initiation of aseptic cultures, comprehensive knowledge of plant species' physiological state and susceptibility to different pathological contaminants is required (Pati et al., 2006). The procedure commonly adopted in most studies involves first surface sterilisation of the explants with 70% (v/v) ethanol for 20–30 seconds, followed by 5–7 minutes with 0.1% HgCl2, and finally rinsing in sterile distilled water (Rout et al., 1989, 1991, 1999; Skirvin et al., 1990). Khosh-Khui and Sink (1982), Skirvin and Chu (1979), and Hasegawa (1979) carried out sterilisation of shoot tips using sodium hypochlorite (5.25%) and "Tween 20" or Triton X (0.1%) in their studies.

In our study, single-node internode pieces with a thickness of 0.4-0.6 cm and a length of approximately 1-1.5 cm, taken from the green shoots of two different varieties of commercially produced hybrid tea rose (R. hybrida) plants (Lady Rosa and Hybrid rose), were used as explant sources. The green shoots were cut into pieces, with one node on each, after removing the leaves on them. For sterilisation of the separated shoot parts, (1) wash and rinse under running tap water for 15 minutes, (2) keep it in 70% ethyl alcohol for 30 seconds, rinse it in pure water three times, (3) shake for 15 minutes in a solution dissolved with 15% commercial sodium hypochlorite (bleach) + 2-3 drops of Tween 20, and then rinse with sterile pure water three times for 5 minutes each. After the final rinse water in the glass jar in which the sterilisation process would be performed was filtered, the shoots were placed on sterile blotting paper; excess water was absorbed into the blotting paper, and the explants were made ready to be transferred to nutrient media. All these processes were carried out under aseptic conditions in a laminar flow cabinet.

The equipment and nutrient media used in the tissue culture study were sterilised in an autoclave at 121 °C and under 1 atm pressure for 15 minutes. The distribution of the nutrient media into the containers was also done in a sterile laminar cabinet with 30 ml in each magenta container.

Sterilised explants were planted in culture vessels containing Murashige and Skoog (MS) nutrient medium containing 30 gL^{-1} sucrose and 7 gL^{-1} agar. In all applications, the pH value of the nutrient media was adjusted to 5.7-5.8, and they were left to grow in the growth chamber at 24±1°C temperature and under 16 hours of light, 8 hours of darkness, and 3000 lux light intensity conditions.

The shoots, which reached a length of approximately 2 cm (at least 1.5 cm) in the nutrient medium in which they were grown, were transferred to the planned shoot medium and propagated. Combinations of growth media (MS, WPM, and AN) prepared by using three different concentrations of 6-benzylaminopurine (BAP) (0, 1, and 2 mgL^{-1}) to use in the shoot propagation stage are given in Table 2. The experiments related to the research were set up with 3 repetitions, 3 culture containers in each repetition, and nine shoots in each culture container. One-way Analysis of Variation (one-way ANOVA) was applied to all data obtained as a result of the study. The relationship between different varieties and medium was determined, and the effect of different medium applications on development was determined by a one-sample t-test.

Table 2: Growth media was used during the shoot propagation phase

Growth media	Combinations of culture media
1.	MS (Murashige and Skoog)
2.	MS + 1 mg L^{-1} BAP
3.	MS + 2 mg L^{-1} BAP
4.	WPM (Woody Plant Medium)
5.	WPM + 1 mg L^{-1} BAP
6.	WPM + 2 mg L^{-1} BAP
7.	AN (Anderson)
8.	AN + 1 mg L^{-1} BAP
9.	AN + 2 mg L^{-1} BAP

The explants taken from the green shoots of the two R. hybrida species we used in our study were grown in MS medium, and the shoots, which reached a size of approximately 2 cm (Figure 2), were cultured in MS, WPM, and AN medium containing BAP at different concentrations. Then the effects of these mediums on shoot development were observed.

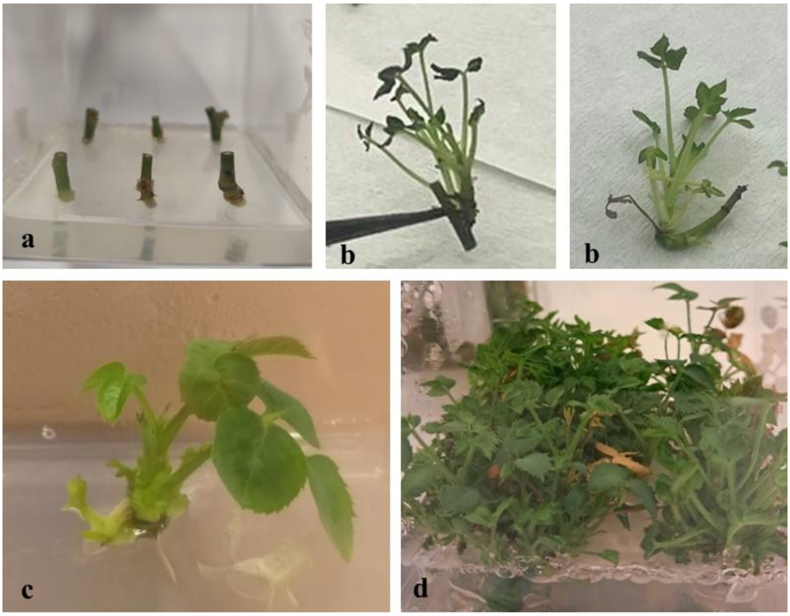

Figure 2: *In vitro* culture stages of *Rosa hybrida*: (a) single-node explant, (b) shoots developing from the node, (c) shoot transferred to different nutrient medium, (d) development of shoots in MS+2 mgL^{-1} BAP medium

The length values and shoot numbers of the grown shoots are presented in Table 2 and Table 3, respectively. When Table 2 and Figure 3 are examined, it is seen that shoot lengths and shoot growth amounts vary depending on the different BAP concentrations and different growth media used. When the data on shoot length and shoot growth amounts are evaluated, it can be said that the MS^{+2} mgL^{-1} BAP combination, in which approximately 50% shoot elongation is observed, is the optimum growth medium (Figure 4).

Table 3: Effect of medium combinations on final shoot length in Lady Rosa and Hybrid Rose cultivars

Medium Combinations	Shoot Length Values (cm)	
	Lady Rosa	**Hybrid Rose**
MS	2.76±0.012	2.77±0.1
MS+1 mg L^{-1} BAP	2.93±0.025	2.8±0.03
MS+2 mg L^{-1} BAP	3.13±0.035	3.15±0.03
WPM	2.72±0.03	2.48±0.02
WPM+1 mg L^{-1} BAP	2.53±0.38	2.73±0.02
WPM+2 mg L^{-1} BAP	2.68±0.24	2.71±0.04
AN	2.75±0.21	2.61±0.013
AN+1 mg L^{-1} BAP	2.83±0.03	2.75±0.02
AN+2 mg L^{-1} BAP	2.76±0.02	2.52±0.02
%CV	**6.012**	**7.160**

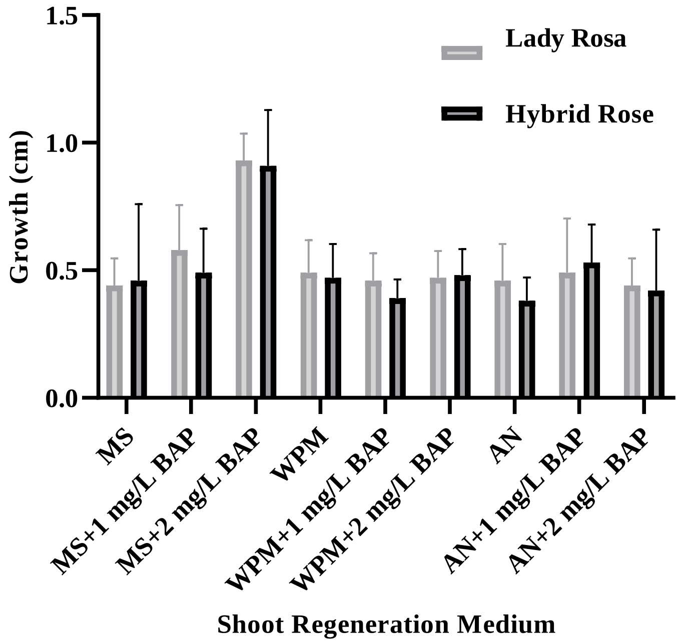

Figure 3: Effect of medium combinations on shoot growth in Lady Rosa and Hybrid Rose varieties

Figure 4: Development of shoots on MS, WPM, and AN media containing different concentrations of BAP

Data on the number of shoots obtained per explant (Figure 5) in MS, WPM, and AN media containing different concentrations of BAP are given in Table 4. When the table is examined, it is seen that the highest number of shoots per explant is in the Hybrid Rose (3.1±0.07) variety grown in the MS^{+2} mgL^{-1} BAP combination, followed by the Lady Rosa variety grown in the same media combination with 2.4±0.035. On the other hand, when the number of shoots developing in WPM and AN media containing different BAP concentrations is examined, it is noted that the number of shoots developing is below 1.

Figure 5: New shoots developing from a shoot grown on MS+2 mgL^{-1} BAP medium

Table 4: Effect of medium combinations on the number of shoots in Lady Rosa and Hybrid Rose varieties

Medium Combinations	Lady Rosa	Hybrid Rose
MS	1.2±0.034	1.3±0.1
MS+1 mg L^{-1} BAP	1.3±0.055	1.5±0.05
MS+2 mg L^{-1} BAP	2.4±0.035	3.1±0.07
WPM	0.6±0.041	0.5±0.042
WPM+1 mg L^{-1} BAP	0.5±0.034	0.6±0.023
WPM+2 mg L^{-1} BAP	0.9±0.034	0.7±0.032
AN	0.8±0.046	1.1±0.029
AN+1 mg L^{-1} BAP	1±0.068	0.8±0.04
AN+2 mg L^{-1} BAP	0.9±0.034	0.9±0.07
%CV	**50.6**	**68.17**

Figure 6: Browning at the base of shoots growing in WPM and AN media containing different concentrations of BAP

Figure 7: Shoots developing in MS, WPM and AN media containing 2 mgL^{-1} BAP

As seen in the photographs in Figure 6 and Figure 7, shoot losses occur in some shoots due to drying from the base. Shoot propagation is the most critical stage of micropropagation. Various studies have reported various factors affecting in vitro shoot proliferation in roses (Pati et al., 2006). These factors are species/genotype/cultivar, growth medium, inorganic salts and organic compounds, carbohydrates, growth regulators, state of the medium (solid, semi-solid, liquid), and physical factors (light, temperature, humidity, and CO_2).

One-way Analysis of Variation (one-way ANOVA) was applied to all data obtained to test whether the different medium combinations we used had the same effect on different *Rosa hybrida* varieties, which were the primary material of our study. The developmental differences between Lady Rosa and Hybrid Rose varieties grown on various media were statistically significant at the $p<0.0001$ level. In addition, when the effect of different growth media containing different BAP combinations for Lady Rosa and Hybrid Rose varieties was evaluated with a one-sample t-test, it was seen that the difference between the growth of individuals of the types in 9 different media was meaningful and significant ($p<0.001$ for both varieties).

3. CONCLUSION

In our study, in which we aimed to obtain shoots from single nodes in MS medium (without growth regulators) and propagate them in MS, WPM, and AN growth medium containing different concentrations of BAP, it was concluded that MS medium containing 2 mgL^{-1} BAP is an appropriate environment for the successful propagation of two different varieties of R. hybrida under in vitro conditions.

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CHAPTER 13

EFFECT OF MAGNETIC FIELD ON PLANT DEVELOPMENT

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INTRODUCTION

The magnetic field (MF) is a constantly encountered environmental factor, and there has been a long-standing debate on the effects of MF on its effect on plant growth and development, as well as and the possibility of using these effects in practice. Recently, studies have reported positive effects of MF on plant growth in general. Research conducted with various plant species and varieties has demonstrated the positive influence of MF on the number of flowers and yield (Danilov et al., 1994; Namba et al., 1995).

All substances possess magnetic properties. A MF arises when electric charges are displaced, that is, when there is a circulation of electric current. Magnetic force also acts on charges moving within a MF. The strength of the magnetic field increase with higher current. Similar to the electric field, the strength of the magnetic field decreases rapidly with distance. The first experimental observations of MFs generated by currents were made by Oersted in 1820. Later experiments by Biot-Savart and Ampere resulted in relations that give the value of the MF at a specific point in the space around a conductor through which current flows (Griffiths 1942).

When examining a piece of magnetic material at an atomic scale, very small currents can be detected. For macroscopic purposes, these current loops are so minuscule that they can treated as magnetic dipoles. Normally. They cancel out each other out due to the random orientation of atoms. However, when a MF is applied, a net alignment of these magnetic dipoles occurs, causing the medium to become magnetically polarized or magnetized. Materials weakly repelled by a magnetic field termed diamagnetic materials, whereas materials attracted to the MF are called paramagnetic materials (Griffiths 1942).

Plants play a crucial role in the survival of all animals and humans. However, in recent times, necessary yields cannot be obtained from plants due various factors, such as the excessive and improper use of chemical drugs, overuse of fertilizers, decreased plant resistance to diseases, and more. One of the main alternative methods to the chemical drugs is the use of magnetic fields. Although the effect of MF on plants are not fully understood, research on this subject continue to increase (Danilov et al., 1994; Namba et al., 1995; Souza et al., 2023).

1. ATOMIC ORIGIN OF THE MAGNETIC FIELD

Due to the spin and orbital angular momentum of charged elementary particles within the atom (electrons, quarks, etc.), a variable electric current is generated, causing each elementary particle behaves like a magnet. The magnetic properties of atoms are primarily determined by the total magnetic moments of unpaired electrons in the other shell of atom's orbitals. When comparing magnitude, the magnetic moment of the nucleus is thousands of times lower than that of the electron. Therefore, in general, the magnetic moment of nucleus cannot be considered significant.

Electrons exhibited two types of motion: motion around their orbits and rotation around their own axes. According to Pauli's principle, there can be at most two pairs of electrons in an orbit. When there are two electrons in an orbit, their spin magnetic moments are opposite to each other (Figure 1). The opposite spin magnetic moments cancel each other out, leaving only the magnetic moments due to orbital motion. If there is only one electron in orbit, it possesses both spin and orbital magnetic moments. According to quantum field theory, when the electron is considered as a dimensionless particle, its spin is analogous to the motion of a disk.

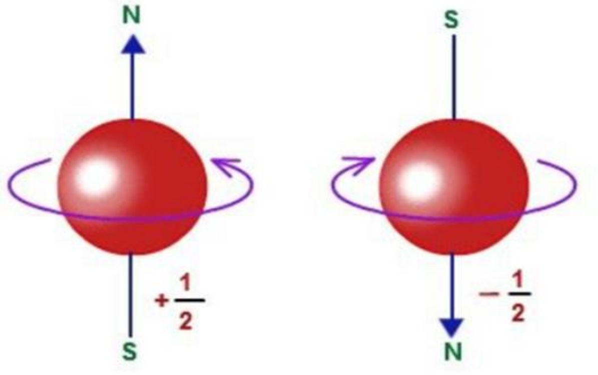

Figure 1: Schematic representation of the spin magnetic moment of the electron.

The electron orbiting around the nucleus forms a large current ring, while the electron spin forms a small current ring. The magnetic moments interact with each other to create the total moment, defining the energy level of the atom or molecule (Figure 2).

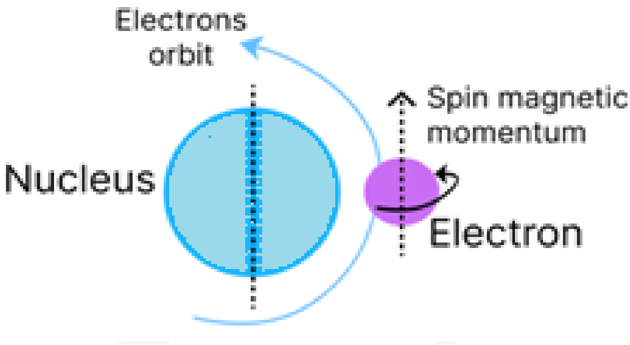

Figure 2: Schematic representation of the total magnetic moment of the electron

Normally, due to the Pauli Exclusion Principle and the tendency to minimize electrostatic repulsion, the enormous number of electrons in a material are paired in orbitals in such a way that their magnetic moments cancel each other out. In other words, to impart net magnetization to magnetic materials, it is necessary to excite the magnetic moments by applying an external MF and to control the temperature of the material. Magnetic materials are classified according to their response to temperature and external MF (Griffiths 1942; Souza et al., 2023).

2. MAGNETIC CLASSIFICATION OF MATERIALS

The best way to illustrate the different types of magnetism is by describing how materials react to a MF. It may be surprising, but all materials exhibit magnetic properties, although to varying degree. The key distinction among these materials lies in the presence or absence of total atomic magnetic moment interaction, whereas in other materials there is a very strong interaction between the atomic magnetic moments. The magnetic behaviour of materials can be classified into five main groups: 1. diamagnetism 2. paramagnetism 3. ferromagnetism 4. ferrimagnetism 5. antiferromagnetism. Materials in the first two groups are magnetically disordered and show no total magnetic interaction, whereas materials in the last three groups exhibit long-range magnetic order below a certain critical temperature (Griffiths, 1942).

Diamagnetic materials are composed of atoms that have no net magnetic moment, meaning their orbital shells are fully filled, and there are no unpaired electrons. Despite this, they show a negative magnetization (magnetization) when exposed to a field, resulting in a negative susceptibility (χ). Elements such as radium, potassium, magnesium, hydrogen, copper, silver, gold, and water belong to the diamagnetic group (Griffiths, 1942).

Most metals are paramagnetic, meaning they are weakly attracted to a magnet. Other metals and non-metals are diamagnetic, indicating that they are weakly repelled by a magnet. Paramagnetic materials possess a net magnetic moment due to unpaired electrons in the partially filled orbits of certain ions or atoms within the material. Iron atoms are one example of atoms with unpaired electrons. However, their magnetic moments interact with each other, and their magnetization becomes zero when the applied field is removed, similar to diamagnetic materials. In the presence of a MF, the magnetic moments of paramagnetic materials partially align in the same direction as the applied field. Resulting in positive magnetization and small positive susceptibility. The effectiveness of the field in aligning the moments is offset by the random selection of temperature effects, leading to temperature-dependent susceptibility. This phenomenon is known as Curie's Law. At normal temperatures and in moderate fields, the paramagnetic susceptibility is known. Elements such as air, aluminium, and silicon belong to the paramagnetic group (Griffiths, 1942; Souza et al., 2023).

Ferromagnetismis a probably commonly associated with material like iron, nickel, cobalt, or their alloys when we think of MF. Unlike paramagnetic materials, the atomic moments of ferromagnetic materials interact very strongly. These interactions are generated by electronic exchange forces, leading to a parallel or antiparallel arrangement of atomic moments. The exchange forces are very large, a quantum mechanical phenomenon, arise due to the relative orientation of the spins of the electrons. Consequently, the magnetic moments of ferromagnetic materials align in parallel, resulting in a significant net magnetization even in the absence of an external magnetic field. Elements such as Fe, Ni, Co and numerous alloys are typically ferromagnetic materials (Griffiths, 1942; De Souza et al., 2023).

In ionic compounds such as ferrimagnetism oxides, more complex forms of magnetic ordering can occur as a result of the crystal structure. One such magnetic arrangement is ferrimagnetism. The crystal structure of ferromagnetic materials consists of regions called domains, each representing a homogeneously magnetically polarized area. When a MF is applied to the sample, the boundaries between these domains shift, causing the domains to move and/or rotate. This sliding and rotational effect leads to a change in the dimensions of the material, a phenomenon known as magnetic field strain. One characteristic of ferromagnetic materials is their ability to change shape when exposed to a MF. This property, also referred to as the Joule effect, was discovered by James Joule in 1842 during his experiments on a nickel sample (Griffiths 1942).

One type of magnetic materials is antiferromagnetic materials, which are the opposite of ferromagnetic materials. While ferromagnets have spin orientations in the same direction, antiferromagnets have spin orientations opposite to each other.

3. EFFECT OF MAGNETIC FIELD ON PLANTS

Plants, like all living organisms, are influenced by magnetic fields from their environment as well as their own magnetic fields during their life processes. At the same time, external MF applications on plants are consciously used today to improve seed quality, increase yield by increasing seedling growth and overall development, and adress deficiencies in seed types through breeding (Pietruszewski, 1993; Ahmet, 2003; Hafeez et al., 2022). The effect of MF applications on plants vary based on on species differences, magnetic field intensities, and exposure durations. Additionally, the response of plant species to magnetic fields varies depending on the seed preparation method and seed characteristics (Dhawi et al., 2009).

In general, due to the complexity of biological systems, it is very difficult to evaluate the effects of magnetic fields on living organisms. Plants are chemically, electrically, and morphologically polar and radially and longitudinally polarized. They ensure intercellular communication by following the ionic flow path in the transmission organs. It has been reported that charge changes in plant structure can cause differences in plants, such as polarization and ion exchange (Zhou, et al., 2006).

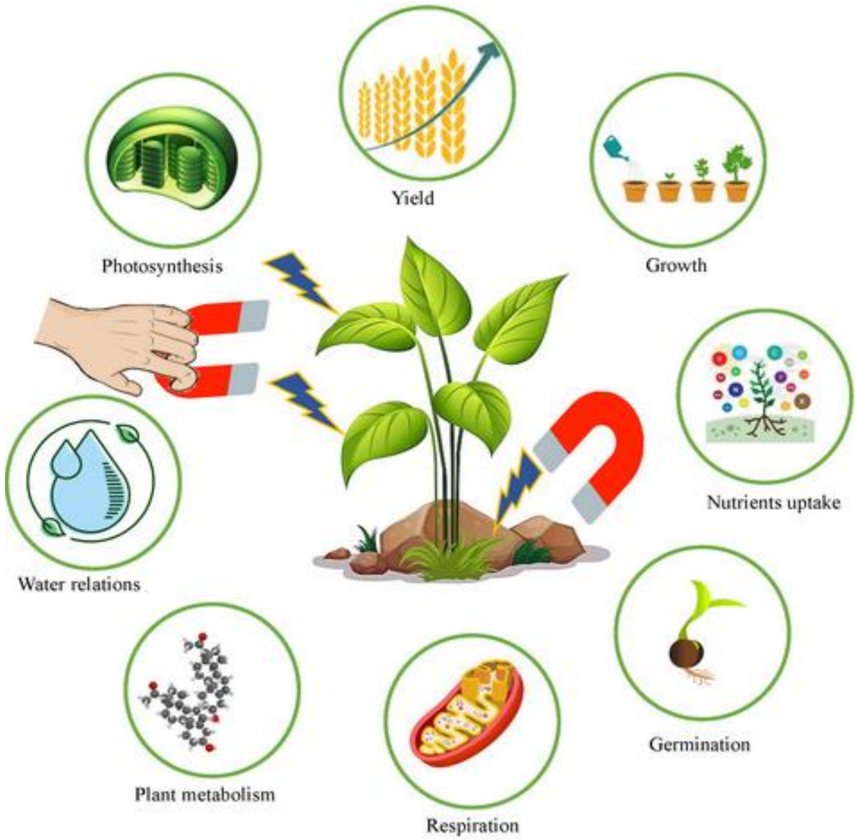

Figure 3: The effect of magnetic field on plants in different ways (Hafeez et al. 2022).

Many studies have been conducted on the effect of MF on plant growth (Dardeniz et al., 2007). In studies conducted with magnetic fields, it has been reported that the yields of different plants such as soybeans, grains and sunflowers are positively affected by MA (Danilov et al., 1994). In a study, it was reported that Komatsuna plants were exposed to a 5 Gauss MF and the germination rate increased (Namba et al., 1995). Martinez et al. (2002) used MF of different intensities on wheat plants and found that plant height and weight increased proportionally with increasing MF intensity. Additionally, Bhatnagar and Deb (1977) applied magnetic field between 0.05 Tesla (T) and 0.30 T to barley, oat and wheat seeds and found that the MF between 0.10 T and 0.15 T had a positive effect on the germination rate and root and shoot length. When some studies on agricultural plants are evaluated, it is stated that

MA provides a 100% increase in wheat seedling height in old studies. Some later studies revealed that the MF effect caused changes in seed germination and affected root development (Audus, 1960). Some other studies have shown that MF applied to the seeds before planting increases the post-germination performance of the plant (Vashisth et al., 2008). Although MF studies on plants are mostly concentrated on agricultural plants, studies have also been carried out on forest tree species in recent years. 3.8-4.8 mT of MF applied to Anatolian black pine (Pinus nigra Arnold.) seeds had a positive effect on seedling length, root length, according to the findings made on the 60th day (Kuzugüdenli et al., 2012).

In some studies, it has been observed that when a MF of appropriate intensity is applied, nutrient absorption and digestion (Kavi, 1977) and photosynthetic activity are encouraged (Lebedev et al., 1975). MF applications applied to the seed during germination cause differences in the germination activity of the seed (Bhatnagar, et al., 1978). MF applied at appropriate intensity and duration changes the water content of the plant (Wooley, 1971); also, chlorophyll level carotenoid level and protein content also vary (Mazza et al., 1999).

In order to explain the effect of MF application on germination, it is recommended to determine the change in α-amylase enzyme activity, which significantly influences germination. In general, higher plants seed store substances such as carbohydrates and proteins in the cotyledon or endosperm. These stored substances are broken down during germination to provide the needed energy. Consequently, a constant supply of carbohydrates, and sugars, which are serve as the embryos energy source, is essential during germination. In seeds, carbohydrates are stored in the form of starch (Luo, et al., 2022).

While the effects of MF effects on plants, animals and humans have been discussed in terms of positive and negative aspects, recent attention has shifted towards fungal and bacterial factors. Understanding the reactions of microorganisms under the influence of magnetic fields is important for determining how they can adapt to stress conditions, and the frequency, duration, and intensity values of magnetic fields on fungal and bacterial factors will play an important role in the control of these factors. This approach, it can be determined whether environmentally friendly plant protection strategies can be developed. İt is worth noting that studies in this area are currently limited (Ružič et al., 1997; Jamil et al., 2012).

Fungi are multiclass organisms with approximately 45,000 species that carry various disease agents for plants and animals. Since fungi do not have chlorophyll organelles, they cannot produce their own food and their nutrition is heterotrophic, saprophytic or parasitic. Diseases caused by fungi are extremely devastating. With the toxins they emit, they negatively affect both the quality and quantity of the crop as well as human health. Destroying fungi or other pathogens without using chemicals in the control of post-harvest diseases in the production sector and especially in organic agriculture is of great importance for the environment and human health. For example, hot water applications, sound waves and MF applications, which are considered as one of the physical combat methods that can be used to combat post-harvest diseases, can be some of the important methods in this regard. Detection of pathogens and defence mechanisms of vegetables and fruits after disease are very important for plant health. For example, when applied physically, radiation, or UV light applications, have the ability to both control the pathogen and penetrate and strengthen the tissues, allowing vegetables and fruits to be preserved for a longer time. Although such chemical-free methods have gained popularity in recent years, the effects of lower and upper doses of these applications on fungal and bacterial agents should be carefully evaluated, and the doses and durations to be applied should be considered in terms of environment and human health. The use of magnetic fields is one of the areas with development potential in this field (Peláez et al., 2013; Ünal et al., 2022; Nagy et al., 2002).

As a result, in studies on magnetic fields applied to plants, different effects have been observed depending on the plant variety, the intensity of the applied MF and the time of application, etc. It has also been shown that some plants' water needs decrease and they become resistant to harmful organisms. More studies are needed to fully understand the effect of the MF on plants and bacteria. However, the effect of the magnetic field on plants is not always positive. Some studies have shown that the application of a MF has no effect or a negative effect on the property under study. The intensity of MF application causes different effects on the studied properties, and in some cases, high intensity MF application has undesirable effects on the studied properties (Abe et al., 1997).

In recent studies, magnetic fields are applied to plant seeds as a pre-planting treatment. It has been observed that these pre-treatments applied before planting increase seed performance (Iqbal et al., 2012; Tahir et al., 2010). Similar studies have shown that the MF applied before planting has a positive effect on the germination percentage, growth rate and germination rate. These results showed that applying a MF to seeds before sowing could be beneficial, especially for seed samples with low germination rates (Pietruszewski et al., 2007). At our university, results like the literature were obtained by applying a single MF intensity or magnetic fields of different magnitudes to different plant seeds. Magnetic fields can be applied to seeds in different ways. Hall Effect Measurement System (HEMS) was used as a MF source in the studies carried out at our university. HEMS is a system that combines a wide magnetic resistance range, high voltage capability, high magnetic field, and wide temperature range to provide the best electronic transport measurement systems available today (Figure 4).

Hall Effect measurements have been an important way to characterize materials since Edwin Hall discovered this phenomenon in 1879. The basic principle is the Lorentz force ($\mathbf{F}=q\mathbf{E}+q\mathbf{V}\times\mathbf{B}$), which is the force on a point charge due to electromagnetic fields. Hall Effect measurements are used in many stages of the electronics industry, from basic materials research and device development to device manufacturing. Users include integrated circuit manufacturers, particularly their technology and process development groups. Crystal manufacturers as well as researchers in university and industry-based laboratories use this measurement technique.

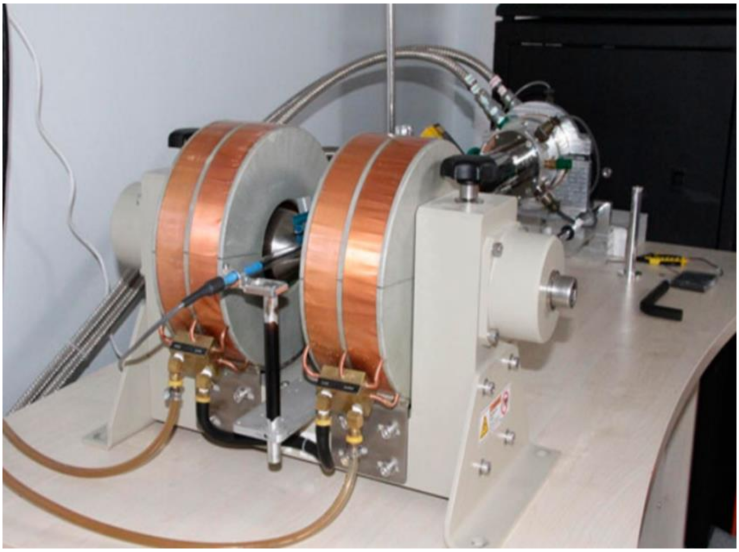

Figure 4: Hall Effect Measurement System (HEMS) with a magnetic field reaching 1.3 Tesla (T).

4. CONCLUSION

Increasing world population, decreasing arable agricultural areas and rapid urbanization have brought about environmental problems. Therefore, under these conditions, new environmentally friendly, fast-reacting methods are needed among plant protection strategies without aggravating the existing situation. Although the importance of chemical control among plant protection strategies is indisputable, reducing the use of pesticides and restricting pesticides with additional technological methods will come to the fore as an environmentally friendly approach. In addition, meeting the water needs of plants due to drought, minimizing product losses due to fungal factors that occur especially after harvest, with the effect of magnetic field, and protecting the product by reducing the number of pesticides used in agriculture are among the issues of great importance. Potentially, applying a magnetic field could be a feasible method for many plant species in the future. Since plants have different genotypes, magnetic field applications cause different responses (such as germination rate, root, and seedling growth) for each plant. More studies are needed to fully understand the effect of the magnetic field on plants and other living things.

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CHAPTER 14

BEST CROP MANAGEMENT AND PROCESSING PRACTICES FOR SUSTAINABLE COTTON PRODUCTION: FIELD TO CONSUMER PERSPECTIVE

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INTRODUCTION

A favorable climate, good agronomic practices, and integrated pest control may all contribute to the development of bountiful crops; as cotton is a perennial shrub native to the subtropics, it can even resist adverse environmental conditions like drought and excessive heat. Cotton yield is affected by several biotic and abiotic variables, which considerably reduces cotton production. Today's dramatic climatological changes have led to weather extremes that directly affect cotton output while also reducing plant development due to numerous pressures in the field environment (Abbas et.al., 2020; Ahmad et.al., 2021; Ahmad and Hasanuzzaman, 2020; Ali et.al., 2020).

Weather and soil conditions, such as temperature, humidity, and rainfall, as well as soil biology and changing physical and chemical characteristics, are the main stressors. These variables often fall into two categories: biotic and abiotic; biotic factors include diseases, weeds, and pests, while abiotic elements include temperature, humidity, and drought, among other things. Pests and infections, among other biotic variables, have a direct impact on the production of cotton and significantly reduced crop yields, which have been estimated to be between 10 and 30 percent. Abiotic variables, on the other hand, such temperature, humidity, and drought, among others, are much worse than biotic stressors and may result in a 50% loss. Although GM cotton (BT cotton), which was originally produced in the middle of the 1990s and is well known for its adaptability, has had great success, agronomic practices and soil system management remain crucial in reducing the stressful field conditions. The connection between crop genetics and agronomy is an important consideration for the sustained production of the cotton crop (Atique-ur-Rehman et.al., 2020; Farooq et.al., 2020; Ghaffar et.al., 2020, 2022; Jabran et.al., 2020).

1. HOW CAN FARMERS MAKE SURE THAT COTTON IS PRODUCED SUSTAINABLY?

Here are a few strategies that farmers and agricultural businesses may use to cultivate cotton using sustainable agriculture.

Figure1: Manually clean cotton picking in progress by a female worker

Reduce the Potential Negative Impacts of Pesticides

Substantial pesticide applications are not needed to protect cotton crops from illnesses. Even if only immature cotton plants are a little bit sensitive and will need the greatest pesticide application, cotton still makes up almost 24% of all insecticides used worldwide. Between 40 and 50 percent of the pesticides used in India are utilized in the growing of cotton.

Precision farming can help farmers preserve their crops more effectively while using fewer toxic pesticides. Through 360-degree monitoring, Smart Risk assists cotton-producing firms in precisely identifying regions with poor crop performance. In addition to boosting agricultural output, it reduces runoff of fertilizer and pesticides, which can pollute water and soil.

Sustainable Use of Freshwater Resources

Cotton is a 'Kharif' crop, making it very tolerant to hot temperatures. It doesn't need a lot of irrigation and is a drought-resistant crop. Most of the water needs of cotton plants may be met by light rainfall or effective irrigation. However, according to data by the Water Footprint Network, India uses 22,500 liters of water on average to produce 1 kilogram of cotton, compared to the 10,000 liters used globally on average. Due to poor water usage and high rates of water pollution from pesticide runoff, there is a discrepancy in water use. A comparable amount of virtual water is lost through exports to other nations due to excessive water use.

Producers can overcome these difficulties with the use of effective water conservation techniques. Additionally, farmers may use Smart Farm to receive precise weather forecasts, schedule irrigation as necessary, and take precautions in case of unfavorable weather.

Improve The Health of Your Soil

Soil-renewing agricultural techniques are encouraged by regenerative agriculture. These include farming a variety of crops all through the year, adding soil armor, and minimizing soil disturbance by lowering tillage. Symbiosis is facilitated by a protective coating of green plant roots that also serves as a natural fertilizer. Like this, techniques like crop rotation, cover crops, and companion crops can aid in the soil's ability to hold onto a balance of various nutrients produced by various plants.

Reduce The Loss of Biodiversity Caused by Agricultural Practices

Reducing tillage and diversifying plant species are just two of the agricultural methods that make up sustainable agriculture, and both are essential to preventing biodiversity loss. Intercropping is another method that can support this goal. To encourage favorable interactions, cotton growers can grow other plants alongside cotton on the same farm throughout this process. To stop soil erosion from wind and water, they can also plant trees with thick roots and cover crops.

Encourage Decent Work for Socioeconomic Growth

Over 250 million people worldwide rely on cotton cultivation as a source of income, accounting for roughly 7% of all employment in developing nations. Production, however, entails maximum risk and little compensation for the farmers. Sustainable cotton production must consider its socioeconomic effects on farmers, their families, and the larger community in addition to its environmental effects.

Concerns about the difficult working conditions faced by agricultural workers, their health and safety, economic instability, the prevalence of child labor or bonded or forced labor, and the treatment of women and girls workers are all included. Numerous global textile and clothing companies back initiatives that guarantee fair and ethical working conditions. The welfare and rights of agricultural employees can be successfully promoted in this respect by introducing traceability to the source.

2. ROLE OF CROP MANAGEMENT PRACTICES IN SUSTAINABILITY

Crop management techniques are essential for advancing agricultural sustainability. Farmers may increase crop yields while minimizing adverse environmental effects, saving resources, and assuring long-term agricultural productivity by putting sustainable crop management strategies into practice. Here are some essential contributions that crop management techniques provide to sustainability:

Soil Health: Maintaining and improving soil health is a key component of sustainable crop management. Crop rotation, cover crops, and conservation tillage are techniques that minimize soil erosion, increase organic matter content, enhance soil structure, and improve soil water-holding capacity. Nutrient leaching is reduced, nutrient cycling is encouraged, and strong plant development is supported.

Water Conservation: For agriculture to be sustainable, especially in areas where water is scarce, effective water management is essential. By giving crops the proper quantity of water at the right time, decreasing water waste, and lowering the danger of water pollution, crop management techniques including precision irrigation, drip irrigation, and soil moisture monitoring assist optimize water usage.

Integrated Pest Management (IPM): Sustainable crop management places a strong emphasis on the application of IPM strategies, which place a high priority on preventing and controlling pests and diseases through biological, social, and environmental measures. IPM minimizes chemical inputs, safeguards beneficial creatures, and upholds a healthy ecological balance by reducing dependency on synthetic pesticides.

Nutrient Management: For the development of sustainable crops, proper nutrient management is crucial. While minimizing nutrient losses to the environment, precision fertilization techniques including soil testing, site-specific nutrient application, and balanced fertilizer usage guarantee that crops receive enough nutrients. This strategy improves nutrient usage efficiency, lowers greenhouse gas emissions, and prevents water contamination.

Energy Efficient Crop Management: Sustainable crop management seeks to lessen dependency on non-renewable energy sources and energy usage. Utilizing energy-efficient technology, such as enhanced machinery, renewable energy sources, and precision agriculture instruments, may help reduce greenhouse gas emissions, reduce fuel usage, and encourage sustainable agricultural practices.

Climate Change Adaptation: Sustainable agriculture depends on crop management techniques that put an emphasis on climate change adaptation. These include choosing crop types that are resistant to climate change, shifting planting dates, modifying irrigation schedules, and putting sensible agricultural diversification techniques into practice. Farmers may reduce risks, preserve production, and promote long-term sustainability by adjusting to changing climatic circumstances (Khan et.al., 2020; Matloob et.al., 2020; Munir et.al., 2020; Noreen et.al., 2020; Rahman et.al., 2020; Ahmad et.al., 2023).

In general, using sustainable crop management techniques is crucial to striking a balance between agricultural output, environmental protection, and societal well-being. Farmers may make a difference in the sustainability and resilience of the agricultural system by putting these practices into practice. They can improve resource efficiency, lessen environmental effects, and improve resource efficiency (Tariq et.al., 2020a, b; Wahab et.al., 2022).

3. CONTROLLING BIOTIC FACTORS

The primary strategy for pest and disease management at the moment is chemical control; most farmers employ synthetic insecticides, fungicides, bactericides, and nematicides, among other things, to prevent pest infestation and control disease. Conventional chemicals are used globally to manage or control illnesses and pests. But the incorrect or careless use of these synthetic pesticides has serious negative effects on the climate generally by endangering the health of people and animals, degrading the ecosystem, causing a problem with insect pest resistance, and killing insects that are not the intended target. Considering this, it is vital to develop some IPM-based pest and disease control strategies that are both successful and environmentally acceptable.

3.1. Integrated Pest Control

IPM stands for Integrated Pest Management, which is a cost-effective and environmentally friendly management strategy for agro-ecosystems that manages pests by employing a variety of control strategies with manipulation in response to demands. The IPM process ends with chemical control. Selective products might be utilized in this program because many pesticides provide serious environmental risks that could have an influence on beneficial insects, human health, and ecosystem health. The three main components of an IPM program are, in general, pest avoidance, post-sampling and monitoring, the preservation of positive factors, and the effective use of chemical and non-chemical pest management measures.

3.2. Avoiding Pests

To effectively avoid pests, one needs have thorough knowledge of the ecology and biology of the specific insect pest in question as well as its behavior. Area-based pest management programs claim that this method has a wider application and is effective against a variety of commodities. Its primary objective is to maintain that pest's population below the economic threshold since if it were to rise over that level, the crop would suffer irreparable harm. It is crucial with this technique to thoroughly research and identify the pest's natural adversaries as well as any potential alternate hosts. Then, management methods might be created based on requirements, serving as the essential building blocks of an efficient management program. The employment of pheromones, semi chemicals, and other biopesticides in combination for mass trapping by interfering with the pest's reproductive cycle must be part of the management methods.

3.3. Cultural Control

According to the agro-based location and climate, cultural pest management is equally important for sustainable cotton production. Prior to the planting of genetically modified cotton, or BT cotton, Pakistan employed delayed planting to control the pink bollworm and lessen infection. Australia avoided planting cotton in the late growing season due to the low yield and increased susceptibility of the crop to bollworm and sucking insect attacks. Helicoverpa armigera was managed by ploughing after the demise of pupae. In Pakistan, early cotton plants had a high concentration of thrips, according to Hussain et.al. (2023). They proposed that by regulating the agronomic elements cotton output could be improved by lowering the thrips infestation since temperature has a beneficial influence in the growth of thrips and other sucking pests. Considering these variables, pre-planned IPM techniques might be created for efficient pest control.

3.4. Rotation of Crops

Another common technique used by many farmers in large-scale cotton agricultural areas is crop rotation. However, depending on the crop chosen, crop rotation can have both beneficial and negative effects on biotic stress factors in various cotton farming systems. In integrated disease management (IDM), selecting the most suitable crops for rotation is crucial to destroying the disease cycle and pest food chain. However, releasing disease-suppressing microorganisms to take control of the illness is still difficult owing to several issues.

3.5. HPR, or host plant resistance

Since cotton plants impart it due to its numerous features, resistance among various insect pests is a growing concern for successful pest management crops. Although the precise mechanism is unclear, certain cotton types with a high leaf hair structure and fewer gossypol glands appear to be resistant to thrips. Similar to certain cotton cultivars, those with leaves resembling okra show some partial resistance to whiteflies. So, developing host plant resistance may also be a successful strategy for controlling insect pests. Detailed biotechnology options for sustainable cotton production are summarized in this regard.

3.6. Pest Monitoring and Sampling

Sampling is a vital step in researching population dynamics and making decisions for efficient pest management methods. For diverse agro farming systems sampling is regarded to be a primary technique. Effective pest control programs depend on accurate sample methods applied at the appropriate times. These methods are also used to examine and assess the effectiveness of management strategies. Whitefly has been successfully controlled in Arizona thanks to the use of appropriate sampling techniques. Due to the widespread cultivation of Bt cotton nowadays, it is possible to preserve beneficial insects (natural enemies) by using effective sampling techniques.

3.7. Use of Insecticides Wisely

The last resort in IPM programs is the use of synthetic insecticides, and even the use of various botanicals and other biopesticides is avoided when spraying in the early cotton season so that the beneficial insects can be preserved. However, relying on and planning the right time and schedule for spraying sprays exclusively with certain chemicals according to their lowest influence on non-target might assist to conserve beneficial insects when the pest population reaches the economic threshold level. The IPM program might benefit from avoiding blind sprays since spot treatments in the field could protect the habitat for beneficial insects.

4. REGULATING ABIOTIC FACTORS

Today, climate change is a major concern that is contributing to a variety of abiotic pressures. Abiotic variables are infamous for their simultaneous occurrence in the environment. In this aspect, prolonged exposure to abiotic stressors ultimately led to decreased yield. While a key characteristic of living things is adaptation. Many plants, notably cotton, have developed defense mechanisms to counteract the effects of abiotic stressors or to minimize the effects of various abiotic elements. Cotton plants' adaptability is dependent on physiological or molecular processes. To combat these extreme environmental stressors, coordinated management is still necessary.

Management of Drought Stress

One of the main factors that prevents the sustainable cultivation of cotton worldwide is drought. To effectively combat the consequences of drought, one must thoroughly understand the soil conditions via extensive study. Commercially farmed upland cotton usually has a favorable relationship with sufficient water availability when planted in dry soils. As a fundamental agronomic practices, farmers that cultivate cotton rely on changed row layout to reduce the impacts of drought stress. While the use of cereal crops in crop rotation improves soil health overall by enhancing the soil's ability to hold water and make it available to the appropriate crop.

When developing new cutting-edge solutions for managing drought stress, botanists who study plant physiology or molecular technologists must bear these considerations in mind. It has been proven scientifically that the only way to effectively combat the impacts of drought and boost cotton output is to make wise use of two extremely important natural resources: soil and water.

Managing temperature-related stress

The issue of climate change is now a global one. While directly producing abiotic stressors, this poses a threat to the environment. Carbon dioxide levels in the atmosphere are too high, which is the major cause of the world's rising temperatures. As a result, the average annual increase in global temperature causes soil moisture to evaporate, which in turn causes drought and salty soil. Although cotton is a tropical crop with the ability to tolerate harsh radiation from the sun, temperature stress directly harms the reproductive and vegetative phases of the plant, resulting in reduced output. This causes the crop to become extremely hot during periods of high solar intensity.

In contrast, some plants exhibit flexible behavior and, in response to temperature stress, produce waxy surfaces that mimic the intense solar radiation. However, the cotton plants reacted by absorbing solar radiation, which heightens osmatic pressure (drought). In this context, varieties with certain desirable characteristics, such as a thick cuticle structure and deep hairs to reduce the temperature or heat stress, may be useful (CICR 2016).

Water stress might be lessened with frequent irrigation. By temperature-sensing remotes, various unique, creative plant-based irrigation systems have recently been developed. The closure of stomata throughout the night, which prevents the cooling action, is the other unfavorable behavior of cotton plants.

In this situation, biotechnologists and plant breeders may concentrate on creating varieties or cultivars that might combat heat stress. Studying the form and function of the roots, as well as the different types of soil, is equally important since they are a crucial component in supplying water to the entire plant. Sandier soils are less able to hold onto water for a long time, which might make them more susceptible to heat and water stress.

Root Morphology's Role in Reducing the Stressors Mentioned Above

According to the kind of soil or plant, management strategies can be used to combat the impacts of the drought. To maximize the use of the resources available, deeper, denser, and stronger plant roots must form. Soil type and condition are crucial in this regard. In the end, this could assist in greatly mitigate the negative effects of heat and drought stress. Whitmore and Whalley provided a thorough explanation of the effects of various dry environments on roots in relation to crop production. According to their thick structure, roots have varied morphologies in the top layer of soil and the sublayer of soil, which may have a significant impact on how plants behave and respond to various stimuli.

Plants having roots that can penetrate deeper or more deeply into the soil are better able to withstand drought stress. The Bollgard Roundup Ready® genetically modified cultivar has a smaller fine root structure than traditional cotton, according to recent Australian research. Fine root output was substantially lower. Bell also discovered that cotton roots get their phosphorus from the subsurface rather than the topsoil. According to a theory, when there is a drought, plant roots may become active in the deeper, bottom layers of the soil while remaining dormant in the topsoil. However, this difficult circumstance finally causes the P resources in Australia's cereal crop soils, where cotton is also produced, to become depleted.

A Soil's Ability to Withstand the Pressures

The incidence of various illnesses, the spread and survival of insect pests, and other biotic and abiotic variables might result in complex situations when it comes to managing such pests and pathogens in connection to various crops. Soil type, structure, and composition may potentially have a negative impact on these variables. In this aspect, the changing soil texture has a significant impact on the connection between plants, soil, and water, resulting in reduced water absorption by plant roots and, eventually, poor plant growth and development. By implementing a variety of technical methods, the negative effects of high temperatures, dry, and salty soils under field might be mitigated.

Modern irrigation systems, improved soil health through various management techniques, agricultural residue management, and cultivar selection are the main components of these efforts. All the aforementioned methods can be used to combat biotic and abiotic stress, but they are not the only ones. Tillage can change the soil's structure in a way that maintains a balance between soil humidity and heat. Therefore, tillage directly affects water penetration via deep soil and transpiration of water from soil to air. Therefore, past research has shown that soils with little or no tillage have a superior structure to withstand these stressors by promoting undisturbed root growth. Deep tillage is required for improved soil structure for farming in some specific situations when the usage of heavy machinery on fields has resulted in a hard or compacted subsoil layer. In conclusion, the creation of stress-tolerant cultivars while bearing in mind the aforementioned elements is vitally required for the integrated control of biotic and abiotic pressures. While describing in full how Pandey et al. (2015) overcame the combined effect of these pressures.

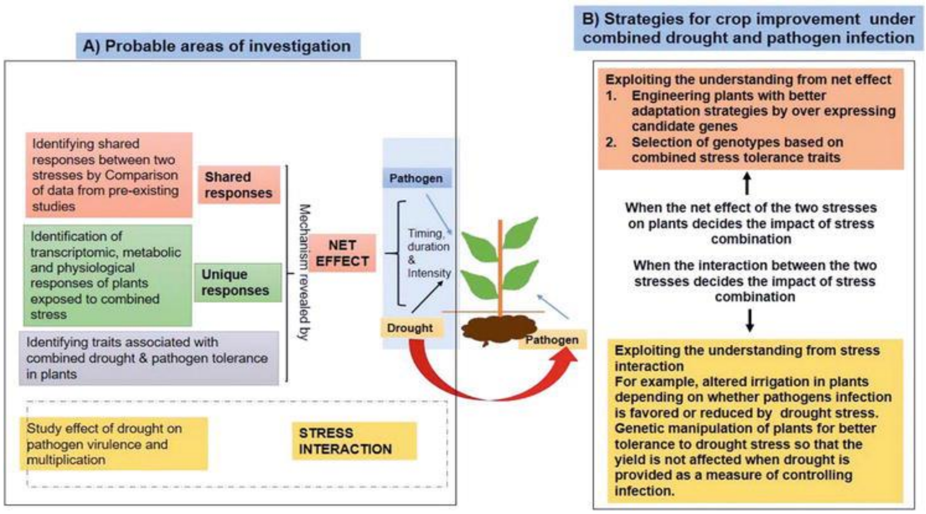

Figure 2: Outline of techniques for enhancing crop production under disease and drought stress (Pandey et al., 2015).

5. CROP YIELDS ARE INCREASED BY STRAW RETURN

Returning combined wheat and cotton straw (Wt-Ct) is the most sustainable management technique, increasing crop yields. There are probably several reasons why straw return has a favourable impact on crop yields. First off, straw return may enhance soil structure by promoting the production of soil aggregates and can control soil aeration and moisture (Laird and Chang, 2013; Gunina and Kuzyakov, 2014), both of which are beneficial for crop growth (Lal, 2007; Wang et.al., 2014). Second, better nutrient availability and SOC are also credited with the beneficial benefits of straw return on crop yields (Chatterjee, 2013; Liang et.al., 2021; Liu et.al., 2021).

6. COTTON FIBER QUALITY PARAMETERS

Cotton fiber quality parameters play vital role in the properties of the final product. Good quality cotton results in fine quality fabric. The most important quality parameters include.

Satple Length

Fibre length or staple length is the most important cotton fibre parameter. It influences the yarn strength. Longer staple length fibers produces stronger yarn. It also positively affect the spinning limit (Klein, 1987). Yarn produced from longer fibre giver better handle feel and luster. Longer length also results reduction in the hairiness of the yarn.

Fibre Fineness

Fibre fineness is the second most important fibre quality parameter. Fibre fineness determines the spinning limit, yarn strength, yarn eveneness and yarn fullness (Gohl and Vilensky, 1985). It also effects the end products drape, lusture and handle.

Fibre Strength

Fibre strength required for any textile fibres is 6 cN/tex. Any fiber having less than 6cN/tex strength is not considered suitable textile fiber (Klein, 1987). Cotton fibre strength is measured in Pressley value. The following scale is used to describe the fiber strength.

93 and above	= excellent
87-92	= very strong
81-86	= strong
75-80	= medium
70-74	= fair
Under 70	= weak

7. COTTON YARN SPINNING

Conversion of fibers into yarn is called yarn spinning. Cotton fiber spinning involves following processes.

Blow Room

Blow room is the first department of spinning unit blow room organizes the mixing method to achieve a homogeneous product of all the different quantities as possible. In blow room cotton is opened, cleaned and mixed. The material from the blow room is fed into the carding machine. The material may be fed in the form of lap or directly by chute feed method. Following operations are performed in the blow room.

(1) Opening;

(2) Cleaning;
(3) Blending/Mixing;
(4) Micro dust removal;
(5) Uniform feed to the carding machine; and
(6) Recycling the waste.

Cardign

Cotton from blow room is transferred into the carding machine (Klein, 2000). The purpose of which is to remove all dirt, sticks, particles of leaves, and other impurities that were not removed in blow room. It disentangles the fibers still more, and lays them approximately parallel. Drawing out the lap into a thin filmy layer of cotton, usually about forty inches wide. After that it contracts this layer into a light, round cotton rope or ribbon about an inch in diameter. This rope is called the card sliver. Carding machine performs the following tasks.

(1) Opening to individual fibers;
(2) Elimination of impurities;
(3) Disentangling of neps;
(4) Elimination of short fibers;
(5) Fiber orientation or alignment;
(6) Elimination of dust;
(7) Fiber blending; and
(8) Sliver formation.

Drawing

The slivers from the carding engine are taken to the drawing frame. About six or eight slivers are introduced together. The drawing frame takes these six or eight and so draws them out that the resulting sliver is no larger than one of the card slivers. Drawing simply mixes the cotton, causes the fibers to arrange themselves in the best manner possible for the spinning that is to follow, and draws the combined six slivers out into the thickness of one. The drawing frame accomplishes this by means of several sets of rollers through which the slivers pass, each following pair of rollers having a higher rate of speed than the pair preceding. Requirements differ, but most cotton is run through drawing frames three times (Klein, 2000). Drawing frame performs the following operations.

(1) Equalizing;
(2) Parallelization;
(3) Blending: and
(4) Dust removal.

Simplex

Next the cans full of sliver from the drawing frames are transferred to the fly frames (simplex frame). Here the cotton is drawn out into still smaller diameters and given the small amount of twist sufficient to allow the sliver to be drawn out further without breaking. The cotton from the fly frames, now called roving, is wound on spools or bobbins and taken to the spinning machines (Klein, 2000). The simplex fame performs the following operations.

(1) Drafting;
(2) Twisting: and
(3) Winding.

Ring Frame

In ring frame the roving is converted into yarn. The yarn has less weight per unit length. Ring is a narrow rectangular shape machine which carries the spindles on both sides of the machine. The roving is directed from the top of the machine after being drafted into the desired count and adequate twist inserted and the yarn is wound on the bobbins (Klein and Stalder, 1987). Ring frame converts the roving into yarn by performing following operations.

(1) Drafting;
(2) Twisting: and
(3) Formation of yarn.

Autocone/Winding

Autocone is one of the most important stage of yarn spinning. Ring bobbins are feeded to the auto cone which delivers a cone. The yarn wound on a ring bobbin is of poor quality. There are also thick and thin places in the yarn. So, winding is done to remove these faults. The Autocone machine detects the faults and remove the faulty yarn and rejoins the ends of the yarn to give a continuous length of fault free yarn. The main objectives of autocone are;

(1) To prepare a bigger package

(2) To remove spinning faults.

Packing

Packing operation is the last department of spinning unit. In this department the cones are stocked for packing and conditioning. After that these are packed according to the requirement of customers. Objectives of packing are;

(1) To avoid deterioration of cones; and

(2) For safe transportation.

8. COTTON FABRIC MANUFACTURING

Warping

Warping is an initial step in fabric preparation during which continuous sheet of many warp ends and wound on weaver beam. Packages are mounted on creel. Warp end later on wound on drum. Lastly, yarn is wound on warper beam. Quality of warping directly determines the loom efficiency and quality of manufactured fabric as it is essential for maintaining warping quality.

Sizing

Sizing step comes after warping and a very critical step. Sizing quality directly impacts the loom performance and woven fabric quality. In this process warp yarn passes through modest tension, yarn stretched and yarn elongation reduced, which is a negative aspect, therefore diverse agents are being used for improving yarn properties.

Weaving

Weaving is defined as “A process in which two sets of yarns (warp and weft) are interlaced at right angle to each other is called as weaving” Weaving is a process in which yarns are interlaced to form a fabric (Sekhri, 2016). The weaving process involved three main steps which are called primary motions.

1) Shedding
2) Picking
3) Beating

Shedding Process

The process of splitting of warp sheet to create an opening for weft insertion is called shedding in weaving process.

Picking

Picking may be defined as the insertion of weft yarn through open shed across the width of the warp sheet with the help of some suitable insertion medium.

Beating

Pushing of dragging the last inserted weft to the fell of cloth with the help of the reed is called beating. Apart from the primary motions there many auxiliary motions which helps in the weaving process. However they only play helping role in the manufacturing of the fabric. The fabric produced is called Greige fabric and is sent to the processing mill for further processing.

9. CONCLUSIONS

In conclusion, sustainable cotton production is crucial in the face of mounting challenges posed by climate change, biotic and abiotic stressors, and environmental concerns. Farmers and agricultural businesses must adopt best crop management practices to ensure the long-term viability of cotton production while minimizing negative impacts on the environment and society.

Integrated pest management (IPM) offers a promising approach to controlling biotic stress factors while minimizing the use of synthetic pesticides. By prioritizing pest avoidance, cultural control, crop rotation, host plant resistance, pest monitoring, and the preservation of beneficial insect species, farmers can effectively manage pests and diseases without harming the ecosystem.

Abiotic stress factors, such as drought and temperature-related stress, can be mitigated through wise soil and water management. Crop rotation, deep-rooted cultivars, and innovative irrigation systems are key strategies in this regard. Additionally, soil quality and tillage practices play a crucial role in enhancing stress tolerance.

The adoption of sustainable crop management techniques, including soil health maintenance, water conservation, nutrient management, and energy-efficient practices, is essential for achieving a balance between agricultural productivity and environmental sustainability. These practices not only improve resource efficiency but also contribute to climate change adaptation. Furthermore, sustainable cotton production should not only focus on environmental aspects but also consider the socio-economic well-being of farmers and laborers. Fair working conditions, traceability, and ethical practices in the cotton industry are essential for ensuring decent work for all stakeholders.

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